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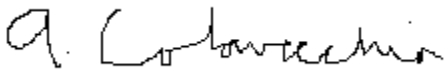

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EFFECTIVENESS AND SAFETY OF FOUR-FACTOR PROTHROMBIN COMPLEX AND FRESH FROZEN PLASMA IN CARDIAC SURGERY

by

A. CARMINE COLAVECCHIA

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EFFECTIVENESS AND SAFETY OF FOUR-FACTOR PROTHROMBIN COMPLEX AND FRESH FROZEN PLASMA IN CARDIAC SURGERY

To the Faculty of the University of Houston, College of Pharmacy:

The members of the committee appointed to examine the dissertation of *A. Carmine Colavecchia* find it satisfactory and recommend that it be accepted on September 6, 2017.

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Dedication page

To my mom for her unwavering love and support.

ABSTRACT

EFFECTIVENESS AND SAFETY OF FOUR-FACTOR PROTHROMBIN COMPLEX AND FRESH FROZEN PLASMA IN CARDIAC SURGERY

Objectives: The purpose of this study was to (i) describe the utilization pattern of four-factor prothrombin complex concentrate (4PCC) and fresh frozen plasma (FFP) used intraoperatively in coronary artery bypass graft (CABG) and valve surgeries requiring cardiopulmonary bypass (CPB) (ii) evaluate the factors associated with use of 4PCC or FFP intraoperatively in CABG and valve surgeries requiring CPB (iii) evaluate the effectiveness of 4PCC used intraoperatively in CABG and valve surgeries requiring CPB (iv), and assess the safety of 4PCC used intraoperatively in CABG and valve surgeries requiring CPB.

Methods: This retrospective, cohort study identified all CABG, valve repair, and valve replacement surgeries from March 2014 to April 2016 at Houston Methodist Hospital (HMH), Houston, Texas. Patients included in the study were 18 years of age or older and receiving CABG and/or valve surgery requiring CPB. Patients who received other cardiac procedures during the CABG or valve procedure were excluded as well as patients receiving both FFP and 4PCC intraoperatively. The data sources for this study included institutional electronic health records (EHR), claims from Vizient, and clinical measures, comorbidities, and outcomes from the Society of Thoracic Surgeons (STS). The 4PCC and FFP exposures were identified from charge claims extracted from the Vizient database and validated from the EHR. Descriptive statistics were performed to assess the utilization pattern of 4PCC and FFP used intraoperatively in CABG and valve procedures, and three multivariable logistic regression models were created to determine the predictive factors of using 4PCC or FFP intraoperatively. The independent variables in the multivariable models were selected based on the Andersen Behavior Model and hypothesized that predisposing, enabling, and need factors that influence the use of these agents. The dependent variables in these logit models were the exposure of 4PCC, FFP, or 4PCC versus FFP. The

primary endpoint evaluating the effectiveness of 4PCC versus FFP was the proportion of patients who received a red blood cell (RBC) transfusion intraoperatively or within 24 hours postoperatively. Multivariable logistic regression using backward elimination was performed to determine the effectiveness of 4PCC versus FFP administered intraoperatively with the dependent variable as RBC utilization. A sensitivity analyses on the primary endpoint was performed by creating a propensity score for the exposures of 4PCC versus FFP, then using the score as a regressor in a logistic regression model to validate the study findings. The safety of 4PCC compared to FFP was evaluated by performing bivariate statistical analysis with a focus on thromboembolic events.

Results: During the study timeframe, a total of 924 patients were identified for the purpose of the study of the 1,946 patients who underwent CABG and/or valve surgery; 690 patients (70.2%) did not receive FFP or 4PCC intraoperatively (control), 166 patients (16.9%) received 4PCC only, 68 patients (6.9%) received FFP only, and 58 (5.9%) received both 4PCC and FFP intraoperatively. . More patients in the control and FFP groups underwent CABG alone (Control: 329 (56.8%); FFP: 33 (48.5%), and less patients in the control and FFP groups had valve procedures alone compared to the 4PCC group (Control: 247 (35.8%); FFP: 27 (39.7%). The control group also had significantly less repeat open-chests compared to the FFP and 4PCC groups (Control: 68 (9.9%); FFP: 14 (20.6%), 4PCC: 40 (24.1)). In addition, the control group had significantly shorter surgeries, CPB time, aortic cross-clamp time (ACT), and required less cell saver units compared to the FFP and 4PCC groups, while the FFP and 4PCC groups did not differ on any of the aforementioned measures.

Factors positively associated receiving 4PCC compared to the control included the predisposing factor age (years) and need factors like international normalized ratio (INR), cell saver use (units), CPB time (min), and desmopressin use, and need factors negatively associated receiving 4PCC compared to the control included body mass index (BMI) (kg/m^2), hematocrit (HCT) (%), platelets greater than 150 $10^9/L$, cardiac arrhythmia, dyslipidemia, and ε-aminocaproic acid (EACA) intraoperative use. Need

factors associated with an increase in the odds of receiving FFP compared to the control were patients undergoing an emergent procedure, history of cerebrovascular disease (CVD), and cell saver use (units). Lastly, patients were more likely to receive 4PCC compared to FFP with each unit increase in cell saver use, if desmopressin was administered intraoperatively, and if the patient had HTN. Factors decreasing the likelihood of receiving 4PCC compared to FFP were patients that had dyslipidemia, liver dysfunction, and HCT (%).

In the unadjusted bivariate comparison of patients requiring RBC transfusion, patients receiving 4PCC compared to FFP required less RBC transfusions intraoperatively and/or within 24 hours postoperatively (OR=0.43; 4PCC: 100/166 (60%) vs. FFP: 53/68 (78%); p-value=0.01). For the primary endpoint, the multivariable logistic regression model comparing patients receiving FFP intraoperatively to 4PCC found patients receiving 4PCC had a significant reduction in the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.28; 95% CI: 0.13-0.62). The sensitivity analyses revealed patients receiving 4PCC compared to FFP also significantly reduced the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.41; 95% CI: 0.19-0.89).

More patients who received 4PCC had venous thromboembolism (8.4%) compared to the control (2.9%; p-value=0.001) but not compared to the FFP group (2.9%; p-value=0.162). No differences were found in the number of patients who had a stroke/ transient ischemic attack in the control (1.9%), FFP (0%), and 4PCC (3.0%) groups.

Conclusions: This study found approximately 1 out of 5 patients received 4PCC intraoperatively with or without FFP, and approximately 1 out of 14 patients received FFP alone intraoperatively. The study findings suggest that intraoperative use of FFP and 4PCC is mainly occurring in patients with excessive bleeding evidenced by the significant relationship of need factors including cell saver use with their administration. In patients undergoing isolated CABG and/or valve surgery requiring CPB with

indications of excessive bleeding, intraoperative administration of 4PCC compared to FFP can reduce a patient's likelihood of requiring an RBC transfusion intraoperatively and up to 24 hours postoperatively. 4PCC should be used cautiously in hypercoaguable patients or patients with a history of thrombosis and only prescribed in the context of excessive bleeding.

Key words: four-factor prothrombin complex concentrate, fresh frozen plasma, factor concentrate, fibrinogen concentrate, transfusion, coronary artery bypass, valve repair, valve replacement, surgery

ACRONYMS

Acronym	Description
4PCC	four-factor prothrombin complex concentrate
ACT	aortic cross clap time
AKI	acute kidney injury
aPTT	activated partial thromplastin time
BMI	body mass index
CABG	coronary artery bypass graft
CLD	chronic lung disease
CPB	cardiopulmonary bypass
Cryo	cryoprecipitate (15 mL per unit)
CVP	central venous pressure
DBP	diastolic blood pressure
DM	diabetes
EACA	epsilon-aminocaproic acid
FC	Factor concentrate
FFP	fresh frozen plasma (250 mL per unit)
FibC	fibrinogen concentrate
HD	hemodialysis
HF	heart failure
HTN	hypertension
ICU	intensive care unit
INR	international normalized ratio
LOS	length of stay
LVEF	left ventricular ejection fraction
MELD	Model For End-Stage Liver Disease
MI	myocardial infarction
OR	operating room
PAD	peripheral artery disease
PE	pulmonary embolism
Plt	platelet (200 mL per dose)
PNA	pneumonia
RBC	red blood cell (300 mL per unit)
RCT	randomized controlled trial
RRT	renal replacement therapy
SBP	systolic blood pressure
SCr	serum creatinine
SD	standard deviation
TIA	transient ischemic attack
VTE	venous thromboembolism

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CHAPTER I:

EXECUTIVE SUMMARY

STUDY RATIONALE

In the United States more than 300,000 CABG procedures and over 100,000 valve procedures are performed each year.[1] Considering the large volume of these cardiac procedures in the US, cardiothoracic procedures are estimated to use approximately 25% of blood products globally.[2] Major bleeding during and post open-heart surgery requiring cardiopulmonary bypass (CPB) occurs frequently and may result in increased morbidity and mortality, re-exploration post-surgery, and require considerable blood product transfusions. [3-17] Acute blood loss requiring transfusion of blood products (i.e. red blood cells (RBCs) or fresh frozen plasma (FFP)) is associated with increased risk of infection, transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), acute renal failure, thromboembolic events, transfusion-related immunomodulation (TRIM), and allergic/anaphylactic reactions.[3-17]

The aforementioned adverse effects associated with blood product transfusions has led providers to seek other alternative therapies to FFP and allogeneic blood derivatives to mitigate blood transfusion requirements during procedures. Initially approved for the reversal of acute major bleeding caused by vitamin K antagonist therapy, four-factor prothrombin complex concentrate (4PCC) contains a high concentration of lyophilized clotting factors II, VII, IX, X, and protein C and S and rapidly reverses coagulopathy in specific scenarios.[18] 4PCC offers several benefits when used to minimize bleeding compared to FFP that include a faster onset, increased potency, small volume, and ability to administer more quickly due to quick reconstitution.[18] While 4PCC may offer a useful alternative to decrease perioperative bleeding, these products also carry risks including thromboembolic events, infusion-related reactions, hypotension, acute kidney injury, and cost.[18,19]

Since STS last updated its guidelines on blood conservation strategies for cardiac surgery in 2011, the society does not provide specific guidance on the use of PCC versus FFP, except for the urgent reversal of warfarin prior to the procedure.[20] The European Society of Anaesthiologists recommend the use of PCC intraoperatively in the presence of an elevated bleeding tendency and prolonged clotting time, where the adoption of PCC products in clinical practice has increased.[21] With surgery teams having access to both FFP and/or PCC, knowing the factors predicting their administration will assist in establishing best practices for their use and improve future prescribing. Also, no studies have been published comparing the factors predictive of using FFP versus PCC in cardiac surgery. Currently, mixed evidence supports the use of 4PCC compared to FFP to mitigate blood loss in cardiac surgery, and limited comparative data exists regarding 4PCC and FFP in CABG and valve surgery.[22-27]

Overall limited evidence exists regarding the safety and effectiveness of using prothrombin complex concentrates to minimize blood product use intra and postoperatively. The proposed study will provide a significant contribution to the literature, because it offers a real-world analysis regarding the predictive factors for using 4PCC versus FFP as well as the safety and effectiveness of 4PCC compared to FFP in CABG and valve procedures. Only one other nonrandomized study has been published assessing a 3PCC product administered to normocoaguable patients receiving CABG and/or valve procedures in an Italian hospital, and no large randomized or nonrandomized studies have been published assessing 4PCC in CABG and valve procedures.[24]

OBJECTIVES

The objectives of this study were to:

1. Describe the utilization of four-factor prothrombin complex concentrate (4PCC) and fresh frozen plasma (FFP) used intraoperatively in coronary artery bypass graft (CABG) and valve surgeries requiring cardiopulmonary bypass (CPB);

2. Evaluate the factors associated with use of 4PCC or FFP intraoperatively in CABG and valve surgeries requiring CPB;
3. Evaluate the effectiveness of 4PCC versus FFP used intraoperatively in CABG and valve surgeries requiring CPB; and
4. Assess the safety of 4PCC used intraoperatively in CABG and valve surgeries requiring CPB.

MAIN FINDINGS

This retrospective, cohort study identified all CABG, valve repair, and valve replacement surgeries from March 2014 to April 2016 at Houston Methodist Hospital (HMH), Houston, Texas. During the study timeframe, a total of 924 patients were identified for the purpose of the study of the 1,946 patients who underwent CABG and/or valve surgery; 690 patients (70.2%) did not receive FFP or 4PCC intraoperatively (control), 166 patients (16.9%) received 4PCC only, 68 patients (6.9%) received FFP only, and 58 (5.9%) received both 4PCC and FFP intraoperatively. More patients in the control and FFP groups underwent CABG alone (Control: 329 (56.8%); FFP: 33 (48.5%), and less patients in the control and FFP groups had valve procedures alone compared to the 4PCC group (Control: 247 (35.8%); FFP: 27 (39.7%). The control group also had significantly less repeat open-chests compared to the FFP and 4PCC groups (Control: 68 (9.9%); FFP: 14 (20.6%), 4PCC: 40 (24.1)). In addition, the control group had significantly shorter surgeries, CPB time, aortic cross-clamp time (ACT), and required less cell saver units compared to the FFP and 4PCC groups, while the FFP and 4PCC groups did not differ on any of the aforementioned measures.

Factors positively associated receiving 4PCC compared to the control included predisposing factor age (years) and need factors like international normalized ratio (INR), cell saver use (units), CPB time (min), and desmopressin use, and need factors negatively associated receiving 4PCC compared to the control included body mass index (BMI) (kg/m^2), hematocrit (HCT) (%), platelets greater than 150 $10^9/L$, cardiac arrhythmia, dyslipidemia, and ε-aminocaproic acid (EACA) intraoperative use. Need

factors associated with an increase in the odds of receiving FFP compared to the control were patients undergoing an emergent procedure, history of cerebrovascular disease (CVD), and cell saver use (units). Lastly, patients were more likely to receive 4PCC compared to FFP with each unit increase in cell saver use, if desmopressin was administered intraoperatively, and if the patient had HTN. Factors decreasing the likelihood of receiving 4PCC compared to FFP were patients that had dyslipidemia, liver dysfunction, and HCT (%).

In the unadjusted bivariate comparison of patients requiring RBC transfusion, patients receiving 4PCC compared to FFP required less RBC transfusions intraoperatively and/or within 24 hours postoperatively (OR=0.43; 4PCC: 100/166 (60%) vs. FFP: 53/68 (78%); p-value=0.01). For the primary endpoint, the multivariable logistic regression model comparing patients receiving FFP intraoperatively to 4PCC found patients receiving 4PCC had a significant reduction in the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.28; 95% CI: 0.13-0.62). The sensitivity analyses revealed patients receiving 4PCC compared to FFP also significantly reduced the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.41; 95% CI: 0.19-0.89).

More patients who received 4PCC had venous thromboembolism (8.4%) compared to the control (2.9%; p-value=0.001) but not compared to the FFP group (2.9%; p-value=0.162). No differences were found in the number of patients who had a stroke/ transient ischemic attack in the control (1.9%), FFP (0%), and 4PCC (3.0%) groups.

CONCLUSIONS

This retrospective, single-institution study found an increasing number of patients receiving 4PCC compared to FFP to mitigate blood loss in cardiac surgery. Based on the Andersen Behavioral model, predictive factors of administering 4PCC and FFP vary in cardiac surgery, and these factors offer insight into patients' comorbidities and clinical variables associated with their use. In patients

undergoing CABG and/or valve surgery requiring CPB with indications of excessive bleeding, intraoperative administration of 4PCC may reduce a patient's likelihood of requiring an RBC transfusion intraoperatively and up to 24 hours postoperatively compared to patients receiving FFP. 4PCC should be used cautiously in hypercoagulable patients or patients with a history of thrombosis, because 4PCC may increase the risk of thromboembolic events post-cardiac surgery.

IMPLICATIONS OF RESEARCH

By identifying pertinent factors predicting the use of FFP and/or 4PCC, subsequent studies may be performed that target the clinical utility of 4PCC compared to FFP in patients with specific comorbidities such as CVD, liver dysfunction, and HTN. Knowing which patient populations benefit most from 4PCC versus FFP will provide more effective, safer, and individualized care for patients during cardiac surgery.

This study found 4PCC to mitigate blood loss in CABG and valve procedures when patients have excessive bleeding compared to FFP and may offer a viable blood conservation strategy. With our study supporting the results found by Cappabianca and colleagues,[24] institutions need to assess the clinical utility of 4PCC as an alternative blood conservation strategy to FFP in cardiac surgery. Finally, the cost-effectiveness of 4PCC versus FFP for the treatment of excessive bleeding in cardiac procedures needs to be determined to inform payers and institutions about the financial impact of adopting this treatment strategy.

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CHAPTER II:
RISK FACTORS PREDICTING THE USE OF 4PCC AND FFP IN CARDIAC SURGERY

INTRODUCTION

According to a survey performed in 2007, cardiothoracic procedures use an estimated 20% of blood products administered to patients globally.[1] An estimated 50% of patients require a blood transfusion undergoing cardiac surgery and bleeding inevitably occurs from invasive cardiothoracic procedures requiring an open-approach.[2] Furthermore, an estimated 25% of blood product transfusions may be considered inappropriate in coronary artery bypass graft (CABG) procedures.[3] In an effort to minimize allogeneic blood transfusions, many clinicians and researchers have identified best practices for blood conservation strategies as well as studied factors independently predictive of bleeding and patients requiring RBC transfusion.[4-7]

Last updated in 2011, the Society of Thoracic Surgeons (STS) provides evidence-based recommendations for preoperative and perioperative strategies to minimize blood loss and the need for blood transfusion.[4] These recommendations include discontinuation of antiplatelet and anticoagulant agents prior to surgery, red blood cell volume optimization (i.e. erythropoietin use to increase hematocrit (HCT), administration of intraoperative medications that reduce blood loss (i.e. intravenous ε-aminocaproic acid (EACA) or tranexamic acid), and specific recommendations of when to use allogeneic blood products and factor concentrates as well as many other guiding principles. Even when STS's recommendations are followed, several factors are independently associated with bleeding and RBC transfusion in invasive cardiac surgery that are non-modifiable: older age, female gender, lower weight, and emergent or complex operations (redo procedures, operations other than CABG, aortic surgery, etc.).[6-7]

While a large body of evidence provides guidance on predictive factors associated with bleeding and RBC transfusion, little evidence has been published on factors associated with the use of fresh frozen plasma (FFP) and prothrombin complex concentrates. STS does provide guidance to administer FFP when patients experience serious bleeding in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available.[4] In addition, FFP should be included as part of massive transfusion protocols when substantial amounts of red blood cells (RBCs) are administered, which is recommended in massive transfusion protocols regardless of procedure type.[4] On the opposite end of the spectrum, prophylactic use of FFP in cardiac surgery is not recommended, because it does not reduce blood loss or RBC transfusion.[8-9] Thus, the focused use of FFP only in situations of excessive bleeding have resulted in limited research performed to assess factors predicting its use intraoperatively.

Since STS last updated its guidelines on blood conservation strategies in 2011, the society does not provide specific guidance on prothrombin complex concentrate (PCC) versus FFP use, except for the urgent reversal of warfarin prior to the procedure.[4] The European Society of Anaesthiologists recommend the use of PCC intraoperatively in the presence of an elevated bleeding tendency and prolonged clotting time, where the adoption of PCC products in clinical practice has increased.[5] Mixed evidence supports the use of PCC to mitigate blood loss in cardiac surgery, and no studies have been published comparing the factors predictive of using FFP versus PCC in cardiac surgery.[10-15] With surgery teams having access to both FFP and/or PCC, knowing the factors predicting their administration will assist in establishing best practices for their use and improve future prescribing.

Therefore, the purpose of this study was to describe the utilization pattern of four-factor prothrombin complex concentrate (4PCC) and fresh frozen plasma (FFP) use intraoperatively in coronary artery bypass graft (CABG) and valve surgeries requiring cardiopulmonary bypass (CPB) and evaluate factors associated with use of 4PCC or FFP intraoperatively in CABG and valve surgeries requiring CPB.

METHODS

DESIGN AND SETTING

This retrospective, observational, cohort study identified all CABG, valve repair, and valve replacement surgeries from March 2014 to April 2016 at Houston Methodist Hospital (HMH), Houston, Texas. HMH and University of Houston Institutional Review Boards approved the study design and procedures, and HMH waived patient consent for this expedited study. In the Texas Medical Center, HMH is an academic, quaternary care institution with 1,119 licensed beds that serves the greater Houston area and performs more than 1,000 CABG and valve procedures annually.

DATA SOURCES AND COLLECTION PROCEDURE

The data sources for this study included claims data from Vizient, institutional electronic health records (EHR), and clinical measures from Society of Thoracic Surgeons (STS). Vizient clinical database and resource manager was used to identify all CABG and valve procedures performed on patients admitted from March 2014 to April 2016 at Houston Methodist Hospital (HMH). The Vizient membership includes academic health systems from across the country, and these health systems developed the Quality and Accountability Study in order to gather objective, data-driven measures for comparing health systems. The Vizient database provides demographic and claims data as well as proprietary severity of illness and risk adjustment models.

The EHR anesthesia manager was used to gather intraoperative clinical measures for patients receiving CABG and valve surgeries, and preoperative and postoperative measures were gathered from the EHR that were unavailable from STS. From the EHR, the study investigators gathered clinical measures including vital signs, laboratory results, drug exposures and doses, blood product administration, documented blood loss, and timing of these events. These data elements were collected 24 hours prior to the procedure from the EHR, intraoperatively from the anesthesia records, and 24 hours post-operatively from the EHR. Laboratory values collected were hemoglobin, platelets,

fibrinogen, serum creatinine, INR, bilirubin, albumin, and thromboelastography. All anticoagulant and procoagulant agents administered were collected during the aforementioned time windows.

The STS National Database was established in 1989 as an initiative for quality improvement and patient safety among cardiothoracic surgeons. The STS Database contains a large number of clinical, administrative, and diagnostic data elements available to institutions contributing to the dataset. The patient list generated from Vizient was used to identify patients from STS. Variables utilized from the STS database included surgeon, body mass index (BMI), surgery type, CABG count, previous cardiovascular surgeries, patient status preoperatively, comorbidities, anticoagulation prior to surgery, preoperative lab values, and cardiopulmonary bypass time.

The 4PCC exposures were identified from charge claims extracted from the Vizient database and validated from the EHR. A random sample of patients was independently reviewed by two study investigators to ensure the validity of the data collected. Any discrepancies were validated by a third study investigator.

STUDY POPULATION

Patients identified from Vizient included the following ICD-9 procedure codes: 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3619, 351, 3511, 3512, 3513, 3514, 352, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528, 3531, 3532, 3533, and 3732. ICD-10 procedure codes used to identify patients are found in the Appendix (Tables 1-3). The study sample included patients 18 years of age or older receiving open-chest CABG, valve repair, and/or valve replacement requiring CPB. All elective, urgent, and emergent procedures were included in the study. Patients who received other cardiac procedures during the CABG or valve procedure were excluded (i.e. adult congenital cardiac operation, free wall rupture repairs, cardiac tumor removal etc.). Patients receiving both FFP and 4PCC intraoperatively or factor concentrates other than 4PCC and FibC intraoperatively were excluded from the analysis. Patients documented as receiving 4PCC or FFP in the operative anesthesia record were included intervention

groups. Additional exclusion criteria were patients with an unresponsive neurological state prior to procedure, refusal of blood products, previous aortic procedures, resuscitation prior to procedure, robot use during the procedure, circulatory arrest/cooling performed during procedure, pulmonary valve replacement, patients who did not transfer to ICU after care, patients who received factor concentrate within 24 hours preoperatively, or received a factor concentrate within 24 hours post-procedure.

CONCEPTUAL FRAMEWORK: ANDERSEN BEHAVIORAL MODEL

The Anderson Behavioral Model (ABM) of health services research was applied in this study to evaluate factors associated with utilization of 4PCC and FFP intraoperatively during cardiac surgery. ABM was developed almost 50 years ago to characterize why families use specific health services and facilitate the identification of inequitable services.[16,17] Since the creation of ABM, the theory continues to receive modifications that enhance its ability to determine what factors influence healthcare utilization.[14] Noteworthy enhancements to the model include ABM extending to individuals from families, incorporation of system concepts such as healthcare policies, application to consumer satisfaction in the 1970s, and the most updated model includes feedback loops, which gives ABM directionality in relation to the factors influencing a health outcome.[16-19] ABM has been applied to hundreds of different settings including medication prescribing and factors that may predict prescribing and/or utilization of specific medications.[16]

Three principal components comprise ABM: predisposing factors, enabling factors, and need factors. Predisposing factors consist of individual characteristics existing prior to the health service utilization and/or the outcome interest and are not directly responsible for health service use. Common predisposing factors include demographic variables such as age, sex, and race, which were included in our model. Enabling factors facilitate or impede the use of a health service. Enabling factors used to determine 4PCC or FFP administration included the surgeon and the nature of the care (elective, urgent, emergent).[16]

Finally, need factors represent more immediate determinants of using a health service. Need factors consist of an array of variables such as diagnostic results, laboratory values, comorbidities, and functional status. Need factors included in our model included many comorbidities, pertinent laboratory values prior to surgery, medications affecting coagulation pre and postoperatively, and other factors that influence the patients' coagulation status intraoperatively.[16]

SURGICAL PROCEDURE AND OPERATIVE MANAGEMENT

CABG and valve procedures are conducted via a median sternotomy approach. CPB is initiated in a routine manner involving cannulation of the right atria, vena cava, or femoral vein to oxygenate blood withdrawn from the body and returning the oxygenated blood to the ascending aorta. Anticoagulants and antiplatelets are discontinued as appropriate prior to surgery—if the planned case is elective. Anticoagulation generally resumes within 24 to 48 hours post-surgery unless contraindicated to resume therapy (i.e. active bleeding). At our institution, intravenous heparin is administered at doses of 300 to 400 units per kg to maintain an activated clotting time (ACT) above 450 seconds prior to the procedure. After the induction of anesthesia, patients receive a standard infusion of intravenous ε-aminocaproic acid (EACA) 10 gram bolus, followed by a 10 gram infusion during the procedure, and a 5 gram bolus at the end of the surgery. When CPB is ceased, protamine sulphate is administered 1 mg per 100 units of heparin given during the procedure. Patients with prolonged ACT after surgery will received additional protamine as necessary for reversal of heparin effects. After the reversal of heparin, the anesthesiologist and surgery team will visually inspect the surgical field for major bleeding and/or microvascular bleeding to determine if blood products—RBCs, FFP, platelets, and/or factor concentrates (4PCC and/or FibC)—are warranted as well as perform thromboelastography (TEG) if necessary. The TEG results are used to guide the administration of allogeneic blood products. Thus, the various modalities used to cease bleeding and restore hemostasis are individualized. The use and administration of factor concentrates and allogeneic blood products is not protocolized at our institution, and providers may use either

allogeneic blood products or factor concentrates as per their clinical judgment. Other elements considered prior to administration of these treatment modalities includes prothrombin time, activated partial thromboplastin time, platelet count, hemoglobin, and hemodynamics. After open-chest CABG and valve procedures, patients are transferred to the cardiovascular intensive care unit for management.

The 4PCC product used exclusively at HMH is Kcentra (CSL Behring; Marburg, Germany), and the FibC product used exclusively is RiaSTAP (CSL Behring; Marburg, Germany). Kcentra was approved in April of 2013, and RiaSTAP was approved in January of 2009. The use of these products intraoperatively began in January to February 2014 for CABG and valve surgeries. Kcentra is supplied in 20 mL vials with approximately 500 units of Factor IX. The product is reconstituted with 2 diluents supplied with the medication. Kcentra is administered intraoperatively slow intravenous push following the maximum rate of the package insert of 210 units per minute. RiaSTAP is supplied in 50 mL vials with 900 to 1300 mg of lyophilized fibrinogen concentrate powder. RiaSTAP is reconstituted with 50 mL of sterile water and is administered slow intravenous push as recommend by the package insert.[20,21]

STUDY VARIABLES AND DEFINITIONS

This study evaluated factors associated with use of 4PCC or FFP intraoperatively in CABG and valve surgeries requiring CPB. Three models were created to determine the predictive factors of administering 4PCC or FFP intraoperatively. The dependent variable in each of these logit models was the dichotomous exposure of 4PCC (0=no, 1=yes), FFP (0=no, 1=yes), or 4PCC versus FFP (FFP=0, 4PCC=1).

As previous described, the independent variables were selected based on the Andersen Behavioral Model and divided into the three primary categories of the model: predisposing, enabling, and need factors. These included:

<u>Predisposing factors</u>

1. Age: Age was modeled continuously by year of age.

2. Sex: Sex was categorized for male (0) and female (1).
3. Race: Self-reported race was categorized as white (0), black (1), Asian (2), and other (3).

Enabling factors

1. Surgeon: Surgeons performing the surgeries were categorized based on each individual with one combined variable for surgeons performing surgeries less often (surgeon other).
2. Preoperative status (emergent/urgent or elective): Preoperative status was dichotomized as elective (0) or emergent/urgent (1).

Need factors

1. Combined CABG + valve procedure: Patients who received CABG plus a valve surgery were categorized as 1 if yes or 0 if no.
2. Previous open chest procedure: Patients with previous open chest procedures were categorized as 1 if yes or 0 if no.
3. Body mass index (BMI): BMI was modeled as continuous variable in kg/m^2.
4. Comorbidities were based on documentation from STS and dichotomized as 1 if present and 0 if not.
    a. Arrhythmia: Patient was considered as having an arrhythmia if the patient had a history of a cardiac rhythm disturbance before the start of the operative procedure which includes the institution of anesthetic management.
    b. Coronary artery disease (CAD): Patient was considered as having coronary artery anatomy and/or disease if documented and available prior to surgery.
    c. Cerebrovascular disease (CVD): Patient was considered to have CVD if any of the following were present prior to the procedure:

i. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours.

ii. TIA: Defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction, where the neurological dysfunction resolves within 24 hours.

iii. Noninvasive or invasive arterial imaging test demonstrating >=50% stenosis of any of the major extracranial or intracranial vessels to the brain.

iv. Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy.

d. Diabetes mellitus (DM): Patient was considered to have DM if diagnosed and/or treated by a healthcare provider in the past.

e. Dyslipidemia: If the patient had a history of dyslipidemia that was diagnosed and/or treated by a physician.

i. National Cholesterol Education Program (NCEP) criteria include documentation of the following:

1. Total cholesterol >200 mg/dL (5.18 mmol/L); or
2. LDL >=130 mg/dL (3.37 mmol/L);
3. HDL <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.30 mmol/L) in women;
4. Currently receiving antilipidemic treatment.

f. Heart failure (HF): Patient has a history of heart failure occurring more than 2 weeks prior to current episode of care.

g. Hypertension (HTN): If the patient had a current diagnosis of hypertension defined by any 1 of the following:

    i. History of hypertension diagnosed and treated with medication, diet, and/or exercise.

    ii. Prior documentation of blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mm Hg systolic or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease.

    iii. Currently undergoing pharmacological therapy for treatment of hypertension.

h. Immunocompromised: Indicates whether the patient was immunocompromised due to immunosuppressive medication therapy within 30 days preceding the operative procedure or existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy, inhaled steroid therapy or pre-procedure protocol.

i. Liver dysfunction: Patient had a history of hepatitis B, hepatitis C, cirrhosis, portal hypertension, esophageal varices, chronic alcohol abuse or congestive hepatopathy, excludes NASH in the absence of cirrhosis.

j. History of myocardial infarction (MI): The patient had at least one documented previous myocardial infarction at any time prior to this surgery.

k. Peripheral artery disease (PAD): Patient had a history of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems).

l. Pneumonia (PNA): Patient was considered to have a history of PNA if the patient had a recent (within 30 days) or remote (more than 30 days) history of PNA.

5. Anticoagulation received within 48 hours of procedure: Patients who received anticoagulation within 48 hours of procedure that was an intravenous and/or subcutaneous anticoagulant.
6. Antiplatelet received within 5 days of the procedure: This variable indicated whether a patient received an antiplatelet within 5 days preceding surgery.
7. Aspirin use prior to the procedure: This variable indicated whether a patient received aspirin or Ecotrin within 5 days preceding surgery.
8. Categorized central venous pressure (CVP): Patient's central venous pressure was documented immediately prior to incision time and categorized as 0-3 (1), 4-9 (0), 10-15 (2), and > 15 (3).
9. Hematocrit (HCT) % prior to the procedure: HCT was modeled as a continuous variable and gathered within 24 hours of the procedure.
10. Left ventricular ejection fraction (LVEF) prior to the procedure: Last documented LVEF prior to induction of anesthesia. LVEF was modeled as a continuous variable.
11. Dichotomized platelet count: The platelet count closest to the date and time prior to surgery. This variable was dichotomized to platelets greater than or equal to 150 (1) and less than 150 10^9/L (0).
12. Serum creatinine, mg/dL (SCr) prior to the procedure: The SCr closest to the date and time prior to surgery and was modeled continuously.
13. Cell save use (units): The documented amount of cell saver units recycled intraoperatively and modeled continuously.
14. Cardiopulmonary bypass (CPB) time (min): The total number of minutes that systemic return was diverted into the CPB circuit and returned to the systemic system.

15. Intraoperative antithrombin III use: Documented intraoperative administration of antithrombin III, 1 if given and 0 if not given.
16. Intraoperative desmopressin use: Documented intraoperative administration of desmopressin, 1 if given and 0 if not given.
17. Intraoperative ε-aminocaproic acid (EACA) use: Documented intraoperative administration of EACA, 1 if given and 0 if not given.

Variables represented in the patient's baseline characteristics but not included in the models were cancer, chronic lung disease, hemodialysis, inotrope administration prior to procedure, intraoperative fibrinogen concentrate, and aortic cross-clamp time (ACT). Cancer, chronic lung disease, intraoperative fibrinogen concentrate, and inotrope administration prior to procedure were excluded due to the small sample size in the study groups. SCr allowed for patients undergoing hemodialysis to be indirectly controlled for in addition to mild and moderate chronic kidney disease. Finally, aortic cross-clamp time and surgery duration were strongly collinear to CPB and not included in the model.

STATISTICAL ANALYSIS

Descriptive statistics and bivariate analysis were used to compare the study samples: patients exposed to 4PCC, patients exposed to FFP, and patients not exposed to 4PCC or FFP. Two-tailed bivariate analysis was performed using student's t-test for continuous parametric data, Wilcoxon rank-sum test for continuous non-parametric data, and chi-square test or fisher's exact for proportional data. A p-value of < 0.05 was accepted as indicating a statistical significance. Comparisons across the 3 study groups were not performed, because differences across the study groups were not of interest.

Multivariable logistic regression analyses were used to determine the predictors of intraoperative use of 4PCC or FFP. In the 4PCC model, patients who received FFP intraoperatively were excluded and vice versa for the FFP model. In addition, a multivariable logistic model was created that included only FFP and 4PCC exposed patients to determine what factors predicted 4PCC versus FFP use.

In the model comparing FFP and 4PCC, a backward elimination function was used to determine the predictive factors of using of 4PCC versus FFP administered intraoperatively. Backward elimination was chosen to create a parsimonious model due to the smaller sample size including only FFP and 4PCC patients.[22] Compared to other variable selection techniques in regression, backward elimination offers the advantage of decreasing the likelihood of omitting important negatively confounded sets of variables, because all variables are included in the initial model.[22,23] In addition, backward elimination function performs as well as other stepwise/elimination functions based on simulation studies.[21] All confounding variables found to be significant at p-value < 0.2 in a backward elimination function were included model comparing 4PCC to FFP.[22,23]

The dependent variable for these models were dichotomous variables of FFP (0=no exposure, 1=exposure), 4PCC (0=no exposure, 1=exposure), and FFP versus 4PCC (0=FFP, 1=4PCC), respectively. Independent variables were selected a priori based on the ABM model of health service utilization (predisposing, enabling and need factors). The mathematical expression of the logistic regression model is:

$$\log (p/1-p) = \beta 0 + \beta 1\, X1 + \beta 2\, X2 + \ldots + \beta k\, Xk$$

Where X1..... Xk were predictor variables (predisposing, enabling and need variables), and p was the probability of the occurrence of the exposure—FFP or 4PCC. Beta coefficients were exponentiated to provide odds ratios in order to interpret factors associated with FFP or 4PCC use.

A p-value of less than 0.05 was accepted as indicating a statistical significance in the multivariable models and bivariate statistical tests. The discrimination of each multivariable model was determined by calculating the C-statistic, and the calibration of the model was determined by performing the Hosmer-Lemeshow test. A p-value of greater than 0.05 for the Hosmer-Lemeshow test indicates a good fit. Statistical analyses were performed using SAS 9.3, SAS Institute, Cary, NC.

RESULTS

UTILIZATION OF 4PCC AND FFP USE IN CARDIAC SURGERY

During the study timeframe, 690 patients (70.2%) did not receive FFP or 4PCC intraoperatively (control), 166 patients (16.9%) received 4PCC only, 68 patients (6.9%) received FFP only, and 58 (5.9%) received both 4PCC and FFP intraoperatively. After excluding patients who received both FFP and 4PCC, a total of 924 patients were included in the analysis of the 2,105 patients who underwent CABG and/or valve surgery (Figure 1). The median dose of 4PCC administered to patients was 500 U (9.0 ± 5.8 U/kg), and the median dose of FFP was 2 U (5.9 ± 3.4 mL/kg). More patients in the control and FFP groups underwent CABG alone (Control: 329 (56.8%); FFP: 33 (48.5%), and less patients in the control and FFP groups had valve procedures alone compared to the 4PCC group (Control: 247 (35.8%); FFP: 27 (39.7%). The control group also had significantly less repeat open-chests compared to the FFP and 4PCC groups (Control: 68 (9.9%); FFP: 14 (20.6%), 4PCC: 40 (24.1)). In addition, the control group had significantly shorter surgeries, CPB time, aortic cross-clamp time (ACT), and required less cell saver units compared to the FFP and 4PCC groups, while the FFP and 4PCC groups did not differ on any of the aforementioned measures (Table 1).

PREDICTORS OF 4PCC USE IN CARDIAC SURGERY

Several predictor factors were associated with receiving 4PCC compared to the control (Table 2). The only predisposing factor associated with receiving 4PCC was age (years) (OR: 1.03; 95% CI: 1.01-1.05), and no enabling factors were associated with receiving 4PCC compared to the control. Need factors that increased the odds of receiving 4PCC compared to the control were INR (OR: 16.1; CI: 4.0-64.2), cell saver use (units) (OR: 1.82; CI: 1.49-2.21), CPB time (min) (OR: 1.02; CI: 1.01-1.02), and desmopressin use (OR: 3.51; CI: 2.21-5.57). Need factors associated with a decrease in the odds of receiving 4PCC compared to the control included BMI (OR: 0.94; CI: 0.90-0.98), HCT (%) (OR: 0.91; CI: 0.87-0.96), platelets greater than 150 10^9/L (OR: 0.55; CI: 0.32-0.95), cardiac arrhythmia (OR: 0.55; CI:

0.32-0.95), dyslipidemia (OR: 0.49; CI: 0.28-0.85), and EACA intraoperative use (OR: 0.34; CI: 0.14-0.81). The c-statistic yielded for this model was 0.85, and the Hosmer-Lemeshow test was not significant (p=0.07).

PREDICTORS OF FFP USE IN CARDIAC SURGERY

No predisposing factors were predictive of using FFP compared to the control group. Of the enabling factors in the regression model, patients undergoing an emergent procedure was significantly associated with the administration of FFP compared to the group (OR: 2.23; CI: 1.12-4.48) (Table 3). Need factors associated with an increase in the odds of receiving FFP compared to the control were patients with a history of cerebrovascular disease (CVD) (OR: 2.12; CI: 1.11-4.08) and cell saver use (units) (OR: 1.42; CI: 1.10-1.82). The c-statistic yielded for this model was 0.78, and the Hosmer-Lemeshow test was not significant (p=0.483).

PREDICTORS OF 4PCC COMPARED TO FFP USE IN CARDIAC SURGERY

Of the 34 variables included in the backward elimination model, 14 variables stayed in the regression model (Table 4). No predisposing or enabling factors were significantly associated with patients receiving 4PCC or FFP. Patients were more likely to receive 4PCC compared to FFP with each unit increase in cell saver use (OR: 1.32; CI: 1.08-1.72), if desmopressin was administered intraoperatively (OR: 2.26; CI: 1.14-4.48), and if the patient had HTN (OR: 2.58; CI: 1.01-6.60). Factors decreasing the likelihood of receiving 4PCC compared to FFP were patients that had dyslipidemia (OR: 0.43; CI: 0.19-0.99), liver dysfunction (OR: 0.16; CI: 0.06-0.48), and HCT (%) (OR: 0.92; CI: 0.86-0.98). The c-statistic yielded for this model was 0.75, and the Hosmer-Lemeshow test was not significant (p=0.842).

DISCUSSION

This retrospective cohort study evaluated the utilization of 4PCC and FFP intraoperatively and predictive factors for prescribing 4PCC and FFP in patients that underwent CABG and/or valve surgery requiring CPB. Of the 924 patients that met the study's inclusion criteria, 166 patients (17.9%) received

only 4PCC intraoperatively and 68 patients (7.4%) received only FFP intraoperatively. The median dose of 4PCC administered to patients was 500 U (9.0 ± 5.8 U/kg), and the median dose of FFP was 2 U (5.9 ± 3.4 mL/kg). Based on the Andersen Behavioral Model, predisposing, enabling, and need factors associated with prescribing 4PCC and FFP intraoperatively were identified from 3 multivariable logistic regression models.

Currently, no published studies describe the proportion of patients receiving 4PCC or other factor concentrates in patients that underwent CABG and/or valve surgery requiring CPB. Data on the prescribing rates comparing PCC and FFP are largely unavailable at institutions in the United States, since PCC administration is only indicated for the urgent reversal of warfarin when used in surgery. Furthermore, the STS guidelines for blood management in cardiac surgery were last updated in 2011, and the paucity of new literature published has not been incorporated into their recommendations.[4,10-15] In Europe, the Society of Anaesthiology also recommends the use of PCC intraoperatively in the presence of an elevated bleeding tendency and prolonged clotting time, where the adoption of PCC products in clinical practice has increased.[5] The majority of clinical trials assessing PCC use in cardiac surgery have occurred in European countries, which supports the more widespread adoption in Europe compared to the United States.[10-15]

While the utilization of PCC during cardiac surgery is unknown in the United States, all isolated CABG procedures requiring CPB reported in the STS database were evaluated in 2008 and found 19.3% (95% CI: 19.1%-19.6%) of patients were exposed to FFP intraoperatively. In our study, 29.7% of patients were exposed to FFP and/or 4PCC (including patients who received both 4PCC and FFP excluded from the analysis) intraoperatively or within 24 hours postoperatively.[24] Also, our study included patients that received valve surgery and CABG plus valve surgeries, which require more blood transfusions compared to isolated CABG. As global and national assessments of blood conservation efforts are evaluated in the

future, researchers need to incorporate the utilization of factor concentrates in order to accurately compare institutions.

The doses of 4PCC and FFP administered to patients in our study were similar based on the Factor IX component. The amount Factor IX in 2 U of FFP ranges between 300 to 500 U, and the median dose of 4PCC patients received in our study based on the Factor IX component was 500 U.[25] Compared to other published studies, our patients received lower doses of PCC. In a retrospective study comparing 3PCC to FFP in CABG and valve surgery, the median 3PCC dose was 1,500 U, and median dose of FFP was 2 U—this study did not report weight-based doses.[12] Another retrospective study comparing 4PCC to FFP during pulmonary endarterectomy with hypothermic circulatory arrest used a dose of 15 U/kg of 4PCC and 15 mL/kg of FFP.[13] The labeling for Kcentra® recommends a dosing range of 25 to 50 U/kg for the reversal of acute major bleeding based on the patient's INR.[20] The upper end of this dosing range has resulted in fatal patient cases being reported, and why 4PCC contains a Black Box warning for patients with thromboembolic disease.[20,26] With PCC becoming more widely adopted in cardiac surgery, the optimal dosing strategy for patients remains unknown and requires further investigation to ensure effective and safe doses are selected.

Predictive factors positively associated with 4PCC use compared to the control group were expected: age, INR, cell saver use, CPB time, and desmopressin administration intraoperatively. Of the 5 measures predictive of 4PCC use, the first 4 have been previously found to be associated with blood transfusion.[4-7] Desmopressin was a predictive factor of 4PCC administration likely because of the longer CPB time and greater proportion of uremic ESRD patients resulting in increased platelet dysfunction.[27] Similar to the predictive factors positively associated 4PCC use, the negatively associated factors were anticipated and previously shown to be inversely associated with blood transfusion: BMI, HCT, platelets $> 150\ 10^9$/L, and EACA intraoperative use.[4-7] Two unanticipated factors negatively associated with the use of 4PCC were patients with a history of cardiac arrhythmia and dyslipidemia. Providers may have

been less likely to administer 4PCC in this patient population due to the clotting risk associated with 4PCC and these comorbidities increasing the risk of thromboembolic events.

Comparing the predictive factors of administering FFP to the control, predictive factors positively associated with FFP use were patients requiring an emergent procedure, history of CVD, and the number of cell saver units used. Emergent procedures and cell saver use are independently associated with blood product transfusions, and these factors were expected to be associated with FFP use.[4-7] The significant association with patients having a history of CVD with FFP administration warrants further investigation and previously not shown in other studies.

The multivariable model assessing predictive factors associated with the use of 4PCC versus FFP found several important relationships with respect to need factors. Patients were more likely to receive 4PCC versus FFP as the number of cell saver units used increased, if desmopressin was administered intraoperatively, and if a patient had a history of HTN. While no significant differences were found in the EBL of patients receiving 4PCC versus FFP, it appears 4PCC was given preferentially for patients who required more cell saver use. As previously mentioned, the increased desmopressin use in the 4PCC group may be attributed to the longer CPB time and greater proportion of uremic ESRD patients, which may cause greater platelet dysfunction.[27] Predictive factors negatively associated with using 4PCC were patients with a history of dyslipidemia, liver dysfunction, and HCT. As previously hypothesized, FFP may have been given preferentially to patients with dyslipidemia due to the increase risk of thromboembolic events with 4PCC. FFP contains additional coagulation factors not in 4PCC such Factor XIII and XI and may explain why patients with liver dysfunction were more likely to receive FFP.[25] As HCT increased, patients were less likely to have received 4PCC compared to FFP. This inverse relationship may be due patients requiring more rapid reversal of coagulopathy with lower HCT and why 4PCC was given in this scenario. Of note, the surgeons who performed the procedures were not associated with the use of FFP or 4PCC in any of the multivariable models.

STRENGTHS AND LIMITATIONS

This study provides the first assessment of predictive factors associated with the administration of 4PCC versus FFP during cardiac surgery. Other strengths include the utilization of the STS database, which researchers frequently use to evaluate cardiac surgery quality and safety. This study also collected many clinical variables to determine the relationship with 4PCC and FFP use. Relative to other studies, this study included a large number of patients exposed to 4PCC.

Like all retrospective studies, this study has limitations. While this study included many demographic and clinical variables in the multivariable models, other unmeasured factors in surgery may influence prescribing of 4PCC and/or FFP. The multivariable models evaluated associations and not causal relationships. FibC prescribing could not be isolated from 4PCC versus FFP multivariable analysis, because only 1 patient received FFP. Thus, this FibC variable was excluded from the model. Also, this study did not have access to a robust number of predisposing and enabling factors, which may influence the selection of 4PCC and/or FFP. Finally, this study represents a single institution's practices and needs to be carefully considered before extrapolating to other institutions.

CONCLUSION

This retrospective, single-institution study found an increasing number of patients receiving 4PCC compared to FFP to mitigate blood loss in cardiac surgery. Based on the Andersen Behavioral model, predictive factors of administering 4PCC and FFP vary in cardiac surgery, and these factors offer insight into patients' comorbidities and clinical variables associated with their use. Future studies need to explore the relationship between the predictive factors associated with 4PCC or FFP use and the clinical outcomes in these specific patient populations.

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CHAPTER III:

EFFECTIVE AND SAFETY OF 4PCC COMPARED TO FFP IN CARDIAC SURGERY

INTRODUCTION

Major bleeding during and post open-heart surgery requiring cardiopulmonary bypass (CPB) may result in increased morbidity and mortality, re-exploration post-surgery, and require considerable blood product transfusions.[1-15] Acute blood loss requiring transfusion of blood products (i.e. red blood cells (RBCs) or fresh frozen plasma (FFP)) is associated with increased risk of infection, transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), acute renal failure, thromboembolic events, transfusion-related immunomodulation (TRIM), and allergic/anaphylactic reactions.[1-15] In addition, the process of ordering, receiving, and administering blood products may cause delays in time critical treatment of an acute blood loss.[16]

The aforementioned adverse effects associated with blood product transfusions has led providers to seek other alternative therapies to mitigate blood transfusion requirements during procedures. Initially approved for the reversal of acute major bleeding caused by vitamin K antagonist therapy, four-factor prothrombin complex concentrate (4PCC) contains a high concentration of lyophilized clotting factors II, VII, IX, X, and protein C and S and rapidly reverses coagulopathy in specific scenarios.[17] 4PCC offers several benefits when used to minimize bleeding compared to FFP that include a faster onset, increased potency, small volume, and ability to administer more quickly due to quick reconstitution.[16] While 4PCC may offer a useful alternative to decrease perioperative bleeding, these products also carry risks including thromboembolic events, infusion-related reactions, hypotension, angioedema, and cost.[16,17] An ex vivo study comparing different permutations of factor concentrates products versus allogeneic blood products found factor concentrates to have a more optimal hemostasis profile following cardiac surgery.[18] A small number of experimental and clinical studies have supported

the use of 3-factor prothrombin complex concentrates (3PCC) and other factor concentrate products to minimize bleeding and decreasing the need for blood product transfusions during cardiovascular procedures.[19-24]

Since STS last updated its guidelines on blood conservation strategies for cardiac surgery in 2011, the society does not provide specific guidance on the use of PCC versus FFP, except for the urgent reversal of warfarin prior to the procedure.[20] The European Society of Anaesthiologists recommend the use of PCC intraoperatively in the presence of an elevated bleeding tendency and prolonged clotting time, where the adoption of PCC products in clinical practice has increased.[21] With surgery teams having access to both FFP and/or PCC, limited comparative data exists regarding 4PCC and FFP in CABG and valve surgery.[22-27] The proposed study will provide a significant contribution to the literature, because it offers a real-world analysis regarding the safety and effectiveness of 4PCC compared to FFP in CABG and valve procedures. Only one other nonrandomized study has been published assessing a 3PCC product administered to normocoaguable patients receiving CABG and/or valve procedures in an Italian hospital, and no large randomized or nonrandomized studies have been published assessing 4PCC in CABG and valve procedures.[24]

METHODS

DESIGN AND SETTING

This retrospective, observational, cohort study identified all CABG, valve repair, and valve replacement surgeries from March 2014 to April 2016 at Houston Methodist Hospital (HMH), Houston, Texas. HMH and University of Houston Institutional Review Boards approved the study design and procedures, and HMH waived patient consent for this expedited study. In the Texas Medical Center, HMH is an academic, quaternary care institution with 1,119 licensed beds that serves the greater Houston area and performs more than 1,000 CABG and valve procedures annually.

DATA SOURCES AND COLLECTION PROCEDURE

The data sources for this study included claims data from Vizient, institutional electronic health records (EHR), and clinical measures from Society of Thoracic Surgeons (STS). Vizient clinical database and resource manager was used to identify all CABG and valve procedures performed on patients admitted from March 2014 to April 2016 at Houston Methodist Hospital (HMH). The Vizient membership includes academic health systems from across the country, and these health systems developed the Quality and Accountability Study in order to gather objective, data-driven measures for comparing health systems. The Vizient database provides demographic and claims data as well as proprietary severity of illness and risk adjustment models.

The EHR anesthesia manager was used to gather intraoperative clinical measures for patients receiving CABG and valve surgeries, and preoperative and postoperative measures were gathered from the EHR that were unavailable from STS. From the EHR, the study investigators gathered clinical measures including vital signs, laboratory results, drug exposures and doses, blood product administration, documented blood loss, and timing of these events. These data elements were collected 24 hours prior to the procedure from the EHR, intraoperatively from the anesthesia records, and 24 hours post-operatively from the EHR. Laboratory values collected were hemoglobin, platelets, fibrinogen, serum creatinine, INR, bilirubin, albumin, and thromboelastography. All anticoagulant and procoagulant agents administered were collected during the aforementioned time windows.

The STS National Database was established in 1989 as an initiative for quality improvement and patient safety among cardiothoracic surgeons. The STS Database contains a large number of clinical, administrative, and diagnostic data elements available to institutions contributing to the dataset. The patient list generated from Vizient was used to identify patients from STS. Variables utilized from the STS database included surgeon, body mass index (BMI), surgery type, CABG count, previous cardiovascular surgeries, patient status preoperatively, comorbidities, anticoagulation prior to surgery,

preoperative lab values, cardiopulmonary bypass time, and all other patient outcomes besides allogeneic blood transfusion requirements, which was extracted from the EHR anesthesia record.

The 4PCC exposures were identified from charge claims extracted from the Vizient database and validated from the EHR. A random sample of patients was independently reviewed by two study investigators to ensure the validity of the data collected. Any discrepancies were validated by a third study investigator.

STUDY POPULATION

Patients identified from Vizient included the following ICD-9 procedure codes: 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3619, 351, 3511, 3512, 3513, 3514, 352, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528, 3531, 3532, 3533, and 3732. ICD-10 procedure codes used to identify patients are found in the Appendix (Tables 1-3). The study sample included patients 18 years of age or older receiving open-chest CABG, valve repair, and/or valve replacement requiring CPB. All elective, urgent, and emergent procedures were included in the study. Patients who received other cardiac procedures during the CABG or valve procedure were excluded (i.e. adult congenital cardiac operation, free wall rupture repairs, cardiac tumor removal etc.). Patients receiving both FFP and 4PCC intraoperatively or other factor concentrates other than 4PCC and FibC intraoperatively were excluded from the analysis. Patients documented as receiving 4PCC or FFP in the anesthesia record were included intervention groups. Additional exclusion criteria were patients with an unresponsive neurological state prior to procedure, refusal of blood products, previous aortic procedures, resuscitation prior to procedure, robot use during the procedure, circulatory arrest/cooling performed during procedure, pulmonary valve replacement, patients who did not transfer to ICU after care, patients who received factor concentrate within 24 hours preoperatively, or received a factor concentrate within 24 hours post procedure.

SURGICAL PROCEDURE AND OPERATIVE MANAGEMENT

CABG and valve procedures are conducted via a median sternotomy approach. CPB is initiated in a routine manner involving cannulation of the right atria, vena cava, or femoral vein to oxygenate blood withdrawn from the body and returning the oxygenated blood to the ascending aorta. Anticoagulants and antiplatelets are discontinued as appropriate prior to surgery—if the planned case is elective. Anticoagulation generally resumes within 24 to 48 hours post-surgery unless contraindicated to resume therapy (i.e. active bleeding). At our institution, intravenous heparin is administered at doses of 300 to 400 units per kg to maintain an activated clotting time (ACT) above 450 seconds prior to the procedure. After the induction of anesthesia, patients receive a standard infusion of intravenous ε-aminocaproic acid (EACA) 10 gram bolus, followed by a 10 gram infusion during the procedure, and a 5 gram bolus at the end of the surgery. When CPB is ceased, protamine sulphate is administered 1 mg per 100 units of heparin given during the procedure. Patients with prolonged ACT after surgery will received additional protamine as necessary for reversal of heparin effects. After the reversal of heparin, the anesthesiologist and surgery team will visually inspect the surgical field for major bleeding and/or microvascular bleeding to determine if blood products—RBCs, FFP, platelets, and/or factor concentrates (4PCC and/or FibC)—are warranted as well as perform thromboelastography (TEG) if necessary. The TEG results are used to guide the administration of allogeneic blood products. Thus, the various modalities used to cease bleeding and restore hemostasis are individualized. The use and administration of factor concentrates and allogeneic blood products is not protocolized at our institution, and providers may use either allogeneic blood products or factor concentrates as per their clinical judgment. Other elements considered prior to administration of these treatment modalities includes prothrombin time, activated partial thromboplastin time, platelet count, hemoglobin, and hemodynamics. After open-chest CABG and valve procedures, patients are transferred to the cardiovascular intensive care unit for management.

The 4PCC product used exclusively at HMH is Kcentra (CSL Behring; Marburg, Germany), and the FibC product used exclusively is RiaSTAP (CSL Behring; Marburg, Germany). Kcentra was approved in April of 2013, and RiaSTAP was approved in January of 2009. The use of these products intraoperatively began in January to February 2014 for CABG and valve surgeries. Kcentra is supplied in 20 mL vials with approximately 500 units of Factor IX. The product is reconstituted with 2 diluents supplied with the medication. Kcentra is administered intraoperatively slow intravenous push following the maximum rate of the package insert of 210 units per minute. RiaSTAP is supplied in 50 mL vials with 900 to 1300 mg of lyophilized fibrinogen concentrate powder. RiaSTAP is reconstituted with 50 mL of sterile water and is administered slow intravenous push as recommend by the package insert.[17,25]

STUDY OUTCOMES AND DEFINITIONS

The study evaluated the effectiveness of 4PCC versus FFP used intraoperatively in CABG and valve surgeries requiring CPB. The primary independent variable of interest was use 4PCC and FFP used intraoperatively. The other independent variables were selected based on previous published literature and hypothesized variables that would influence patients receiving an RBC transfusion.[1-7] These included:

1. Age: Age was modeled continuously by year of age.
2. Sex: Sex was categorized for male (0) and female (1).
3. Race: Self-reported race was categorized as white (0), black (1), Asian (2), and other (3).
4. Surgeon: Surgeons performing the surgeries were categorized based on each individual with one combined variable for surgeons performing surgeries less often (surgeon other).
5. Preoperative status (emergent/urgent or elective): Preoperative status was dichotomized as elective (0) or emergent/urgent (1).
6. Combined CABG + valve procedure: Patients who received CABG plus a valve surgery were categorized as 1 if yes or 0 if no.

7. Previous open chest procedure: Patients with previous open chest procedures were categorized as 1 if yes or 0 if no.
8. Body mass index (BMI): BMI was modeled as continuous variable in kg/m^2.
9. Comorbidities were based on documentation from STS and dichotomized as 1 if present and 0 if not.
    a. Arrhythmia: Patient was considered as having an arrhythmia if the patient had a history of a cardiac rhythm disturbance before the start of the operative procedure which includes the institution of anesthetic management.
    b. Coronary artery disease (CAD): Patient was considered as having coronary artery anatomy and/or disease if documented and available prior to surgery.
    c. Cerebrovascular disease (CVD): Patient was considered to have CVD if any of the following were present:
        i. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours.
        ii. TIA: Defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction, where the neurological dysfunction resolves within 24 hours.
        iii. Noninvasive or invasive arterial imaging test demonstrating >=50% stenosis of any of the major extracranial or intracranial vessels to the brain.
        iv. Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy.

d. Diabetes mellitus (DM): Patient was considered to have DM if diagnosed and/or treated by a healthcare provider in the past.

e. Dyslipidemia: If the patient had a history of dyslipidemia that was diagnosed and/or treated by a physician.

    i. National Cholesterol Education Program (NCEP) criteria include documentation of the following:

        1. Total cholesterol >200 mg/dL (5.18 mmol/L); or
        2. LDL >=130 mg/dL (3.37 mmol/L);
        3. HDL <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.30 mmol/L) in women;
        4. Currently receiving antilipidemic treatment.

f. Heart failure (HF): Patient has a history of heart failure occurring more than 2 weeks prior to current episode of care.

g. Hypertension (HTN): If the patient had a current diagnosis of hypertension defined by any 1 of the following:

    i. History of hypertension diagnosed and treated with medication, diet, and/or exercise.

    ii. Prior documentation of blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mm Hg systolic or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease.

    iii. Currently undergoing pharmacological therapy for treatment of hypertension.

h. Immunocompromised: Indicates whether the patient was immunocompromised due to immunosuppressive medication therapy within 30 days preceding the operative

procedure or existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy, inhaled steroid therapy or pre-procedure protocol.

i. Liver dysfunction: Patient had a history of hepatitis B, hepatitis C, cirrhosis, portal hypertension, esophageal varices, chronic alcohol abuse or congestive hepatopathy, excludes NASH in the absence of cirrhosis.

j. History of myocardial infarction (MI): The patient had at least one documented previous myocardial infarction at any time prior to this surgery.

k. Peripheral artery disease (PAD): Patient had a history of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems).

l. Pneumonia (PNA): Patient was considered to have a history of PNA if the patient had a recent (within 30 days) or remote (more than 30 days) history of PNA.

10. Anticoagulation received within 48 hours of procedure: Patients who received anticoagulation within 48 hours of procedure that was an intravenous and/or subcutaneous anticoagulant.
11. Antiplatelet received within 5 days of the procedure: This variable indicated whether a patient received an antiplatelet within 5 days preceding surgery.
12. Aspirin use prior to the procedure: This variable indicated whether a patient received aspirin or Ecotrin within 5 days preceding surgery.
13. Categorized central venous pressure (CVP): Patient's central venous pressure was documented immediately prior to incision time and categorized as 0-3 (1), 4-9 (0), 10-15 (2), and > 15 (3).
14. Hematocrit (HCT) % prior to the procedure: HCT was modeled as a continuous variable and gathered within 24 hours of the procedure.

15. Left ventricular ejection fraction (LVEF) prior to the procedure: Last documented LVEF prior to induction of anesthesia. LVEF was modeled as a continuous variable.
16. Dichotomized platelet count: The platelet count closest to the date and time prior to surgery. This variable was dichotomized to platelets greater than or equal to 150 (1) and less than 150 10^9/L (0).
17. Serum creatinine, mg/dL (SCr) prior to the procedure: The SCr closest to the date and time prior to surgery and was modeled continuously.
18. Cell save use (units): The documented amount of cell saver units recycled intraoperatively and modeled continuously.
19. Cardiopulmonary bypass (CPB) time (min): The total number of minutes that systemic return was diverted into the CPB circuit and returned to the systemic system.
20. Intraoperative antithrombin III use: Documented intraoperative administration of antithrombin III, 1 if given and 0 if not given.
21. Intraoperative desmopressin use: Documented intraoperative administration of desmopressin, 1 if given and 0 if not given.
22. Intraoperative ε-aminocaproic acid (EACA) use: Documented intraoperative administration of EACA, 1 if given and 0 if not given.

Variables represented in the patient's baseline characteristics but not included in the models were cancer, chronic lung disease, hemodialysis, inotrope administration prior to procedure, intraoperative fibrinogen concentrate, and aortic cross-clamp time (ACT). Cancer, chronic lung disease, intraoperative fibrinogen concentrate, and inotrope administration prior to procedure were excluded due to the small sample size in the study groups. SCr allowed for patients undergoing hemodialysis to be were indirectly controlled for in addition to mild and moderate chronic kidney disease. Finally, aortic cross-clamp time and surgery duration were strongly collinear to CPB and not included in the model.

Study outcome definitions

Primary Effectiveness Measures

a. Red blood cell (RBC) transfusion intraoperatively and within 24 hours postoperatively: Documented intraoperative red blood cell (RBC) transfusion by the anesthesiologist and documented RBC transfusion by the nurse within 24 hours post-surgery.

Secondary Effectiveness Measures

b. Intraoperative estimated blood loss (mL)
c. Postoperative hemoglobin (g/dL): Nadir hemoglobin documented in the EHR with 24 hours postoperatively.
d. Postoperative platelets (10^9/L): Nadir platelet count documented in the EHR with 24 hours postoperatively.
e. Fresh frozen plasma (FFP) use within 24 hours postoperatively: Documented FFP transfusion by the nurse within 24 hours post-surgery.
f. Platelet transfusion intraoperatively and within 24 hours postoperatively: Documented intraoperative platelet transfusion by the anesthesiologist and documented platelet transfusion by the nurse within 24 hours post-surgery.
g. Cryoprecipitate transfusion intraoperatively and within 24 hours postoperatively: Documented intraoperative cryoprecipitate transfusion by the anesthesiologist and documented cryoprecipitate transfusion by the nurse within 24 hours post-surgery.

Primary Safety Measures

a. Composite outcome of venous thromboembolism (VTE), pulmonary embolism (PE), stroke/ transient ischemic attack (TIA)), and cardiac arrest during the hospitalization.

Secondary Safety Measures

a. Return to the operating room within 72 hours: Patient returned to OR within 72 hours post-surgery.
b. Reoperation due to a bleed during hospitalization: Patients who were re-explored for mediastinal bleeding with or without tamponade either in the ICU or returned to the operating room.
c. VTE during hospitalization: Patients that developed postoperative venous thrombosis or thromboembolic event during the hospitalization.
d. Renal failure during hospitalization: Patient had acute renal failure or worsening renal function resulting in ONE OR BOTH of the following:
    a. Increase in serum creatinine level 3.0 x greater than baseline, or serum creatinine level ≥ 4 mg/dL (Acute rise must be at least 0.5 mg/dL)
    b. A new requirement for dialysis postoperatively
e. Stroke or TIA during hospitalization:
    a. Patient had a postoperative stroke and the type of stroke (i.e., any confirmed neurological deficit of abrupt onset caused by a disturbance in blood supply to the brain) that did not resolve within 24 hours
    b. Patient had a postoperative Transient Ischemic Attack (TIA): Loss of neurological function that was abrupt in onset but with complete return of function within 24 hours.
f. Length of stay after surgery: Patient's LOS after cardiac surgery.
g. Length of stay: Patient's total LOS including time prior to cardiac surgery.

STATISTICAL ANALYSIS

Multivariable logistic regression analysis was used to control for confounding variables hypothesized a priori that may influence patients receiving RBC transfusion. Using a backward

elimination function, multivariable logistic regression was performed to determine the effectiveness of 4PCC versus FFP administered intraoperatively with the dependent variable as RBC utilization. Backward elimination was chosen to create a parsimonious model due to sample size in this study.[26] Compared to other variable selection techniques in regression, backward elimination offers the advantage of decreasing the likelihood of omitting important negatively confounded sets of variables, because all variables are included in the initial model.[26,27] In addition, backward elimination function performs as well as other stepwise/elimination functions based on simulation studies for the sample size of our study.[27] All confounding variables found to be significant at p-value < 0.2 in a backward elimination function were included model.[26,27] The probability of the outcome was modeled using the logarithmic odds as a linear function of the predictor variables. The mathematical expression of the logistic regression model is:

$$\log (p/1-p) = \beta 0 + \beta 1\, X1 + \beta 2\, X2 + \ldots + \beta k\, Xk$$

Where X1..... Xk were independent variables, and p was the probability of the occurrence of the outcome—RBC transfusion: no (0) or yes (1). Beta coefficients were exponentiated to provide odds ratios in order to interpret factors associated with patients requiring RBC transfusion.

Cappabianca and colleagues methodology is most similar to our methodology and study population. Their study found an effect size of 0.4, and we estimated our population who receives 4PCC or FFP to require RBC transfusion in approximately 70% of patients. Thus, we estimated 198 patents who be required to assess an effect size of 0.4 with 80% power.

To validate the study findings, a sensitivity analyses on the primary endpoint was performed by creating a propensity score for the exposure of FFP (0) versus 4PCC (1). The propensity score was created by developing multivariable logistic regression with dependent variable of FFP (0) and 4PCC (1) that included all factors that may influence FFP and/or 4PCC administration.[26,28] This model allows one to calculate the propensity (probability) of prescribing FFP versus 4PCC, therefore controlling for the

selection bias of administering either agent. All of the aforementioned variables were kept in the multivariable logistic regression model used to generate the propensity score to determine the probability of prescribing 4PCC versus FFP. The probability of prescribing FFP versus 4PCC was used as an independent variable as well as the actual exposure of 4PCC versus FFP in a logistic regression model with the dependent variable of RBC transfusion. The propensity score was evaluated by assessing the overlap of probabilities between the FFP and 4PCC groups.[26,28]

The safety of 4PCC compared to FFP was described by performing bivariate statistical analysis with a focus on thromboembolic events. Multivariable analysis was not performed on the safety endpoints due to the small number of safety events and the effectiveness measures being the primary interest. Descriptive statistics and bivariate analysis were used to compare the study samples: patients exposed to 4PCC, patients exposed to FFP, and patients not exposed to 4PCC or FFP (control). These three groups were not compared across groups but specifically assessed comparing the control to FFP, control to 4PCC, and 4PCC to FFP, because differences across the study groups were not of interest. Two-tailed bivariate analysis was performed using student's t-test for continuous parametric data, Wilcoxon rank-sum test for continuous non-parametric data, and chi-square test or fisher's exact for proportional data.

A p-value of < 0.05 was accepted as indicating a statistical significance in all of the statistical models. The discrimination of each model was determined by calculating the C-statistic, and the calibration of the model was determined by performing the Hosmer-Lemeshow test. A p-value of greater than 0.05 for the Hosmer-Lemeshow test indicates a good fit. Statistical analyses were performed using SAS 9.3, SAS Institute, Cary, NC.

RESULTS

STUDY POPULATION

During the study timeframe, 690 patients (70.2%) did not receive FFP or 4PCC intraoperatively (control), 166 patients (16.9%) received 4PCC only, 68 patients (6.9%) received FFP only, and 58 (5.9%) received both 4PCC and FFP intraoperatively. After excluding patients who received both FFP and 4PCC, a total of 924 patients were included in the analysis of the 2,105 patients who underwent CABG and/or valve surgery (Figure 1). Both the administration of FFP and 4PCC were given towards end of the procedure when patients were taken of CPB (Time given from the end of the procedure for FFP: 1.2 ± 1.0 hours; 4PCC: 1.0 ± 0.5 hours; p=0.109). The median dose of FFP administered intraoperatively was 2 units (IQR: 1-2 units), and the median dose of 4PCC given intraoperatively based on the Factor IX component was 500 units (IQR: 500-1,000 units).

STUDY GROUP COMPARISONS AND UNADJUSTED PATIENT OUTCOMES

Comparison of study groups revealed that more patients in the control and FFP groups underwent CABG alone (Control: 56.8%; FFP: 48.5%; 4PCC: 30.1%), and less patients in the control and FFP groups had valve procedures alone compared to the 4PCC group (Control: 35.8%; FFP: 39.7%; 4PCC: 58.4%). The control group had significantly less repeat open-chests compared to the FFP and 4PCC groups (Control: 9.9%; FFP: 20.6%, 4PCC: 24.1%). In addition, the control group had significantly shorter surgeries, CPB time, aortic cross-clamp time (ACT), and required less cell saver units compared to the FFP and 4PCC groups, while the FFP and 4PCC groups did not differ on any of the aforementioned measures. Comparing the 4PCC and FFP groups, significantly less patients had dyslipidemia and liver dysfunction in the 4PCC group. Also, more patients exposed to 4PCC received concomitant desmopressin and FibC intraoperatively compared to the FFP and controls groups (Table 1).

Bivariate analyses revealed that patients who received intraoperative FFP or 4PCC had similar EBL (FFP: 1382 ± 620 mL; 4PCC: 1459 ± 642 mL; p=0.427), and both had greater EBL compared to the

control group (Control: 1126 ± 459; FFP vs. control p=0.003; 4PCC vs. control p<0.01). The 3 groups' postoperative hemoglobin (Hgb) concentrations significantly differed. The control group's postop Hgb was greater than both the FFP and 4PCC groups (Control: 9.6 ± 1.6 g/dL; FFP vs. control p<0.01; 4PCC vs. control p<0.01), and the 4PCC group had greater postop Hgb than the FFP group (4PCC: 8.9 ± 1.4; FFP: 7.9 ± 1.4; p<0.01). Postoperative platelet counts were similar in the control and 4PCC groups (Control: 123 ± 44 10^9/L; 4PCC: 119 ± 114 10^9/L; p=0.255), and the FFP group had significantly lower platelets compared to both the control and 4PCC groups (FFP: 105 ± 96; FFP vs. control p<0.01; FFP vs. 4PCC p<0.01). The proportion of patients who received a RBC transfusion intraoperatively or within 24 hours postoperatively in control group was significantly less than the 4PCC and FFP groups (Control: 13.6%; Control vs. FFP p<0.01; Control vs. 4PCC p<0.01). Patients who received 4PCC compared to FFP required less RBC transfusions intraoperatively and/or within 24 hours postoperatively (OR=0.43; 4PCC: 60% vs. FFP: 78%; p-value=0.01) as well as required less RBC units (FFP: 2.0 ± 1.7 units; 4PCC: 1.3 ± 1.9 units; p=0.01). Between the FFP and 4PCC groups, no difference was found in the proportion of patients receiving FFP within 24 hours postoperatively (FFP: 8.8%; 4PCC: 10.2%; p=0.814) or receiving cryoprecipitate intraoperatively or within 24 hours postoperatively (FFP: 20.6%; 4PCC: 13.9%; p=0.2). Many differences existed in the secondary outcomes between the control group and the FFP and 4PCC groups (Table 2).

MULTIVARIABLE REGRESSION MODEL AND SENSITIVITY ANALYSIS

For the primary endpoint, the multivariable logistic regression model comparing patients receiving FFP intraoperatively to 4PCC found patients receiving 4PCC had a significant reduction in the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.28; 95% CI: 0.13-0.62). Table 3 includes other factors significantly associated with patients receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively were CVD (OR: 2.53; CI: 1.03-6.21),

HF (OR: 2.10; CI: 1.01-4.37), number of cell saver units transfused (OR: 1.32; CI: 1.00-1.75), and CPB time (OR: 1.03; CI: 1.01-1.04).

The propensity score overlap and distributions are illustrated in Figure 2 and show a moderate degree of overlap based on the probability of receiving FFP versus 4PCC. When including the propensity score as a regressor in the logistic regression model, the sensitivity analyses revealed patients receiving 4PCC compared to FFP also significantly reduced the odds of receiving an RBC transfusion intraoperatively and/or within 24 hours postoperatively (OR: 0.41; 95% CI: 0.19-0.89).

SAFETY OUTCOMES

No difference in the composite safety outcome was found between the study groups (Table 5). More patients who received 4PCC had VTE/PE (8.4%) compared to the control (2.9%; p-value=0.001) but not compared to the FFP group (2.9%; p-value=0.162). No patients in the FFP or 4PCC group experienced a PE, and 2 patients in control group had a PE. More patients returned to the OR within 72 hours postoperatively in the FFP group (13.9%) and 4PCC group (20.6%) compared to the control group (5.4%; p<0.01). No differences were found between the 3 groups in the proportion of patients who had a stroke or TIA in the control, developed renal failure postoperatively, or required reoperation due to a bleed. The control group had a shorter total LOS and postoperative LOS compared to the FFP and 4PCC groups, and the FFP and 4PCC groups postoperative LOS was not significantly different (FFP: 11 (IQR 8-13.5); 4PCC: 11 (IQR: 8-15); p=0.541). Finally, death during the hospitalization was not significantly different between the 3 groups.

DISCUSSION

This retrospective, single-institution study found 4PCC significantly reduced RBC transfusion requirements compared to FFP in CABG and/or valve surgery requiring CPB after controlling for other factors. Bivariate analysis revealed no difference in the composite safety outcome assessing thromboembolic events; however, patients who received 4PCC compared to the control group were

more likely to have a VTE/PE. These findings represent the first real-world evaluation of 4PCC compared to FFP in cardiac surgery in the United States. The use of factor concentrates continues to grow as institutions attempt to develop cost-effective and safe blood conservation strategies. At our institution, surgery teams may administer either 4PCC or FFP to treat excessive bleeding during surgery, which began at the beginning of the study timeframe. The doses of 4PCC and FFP administered in our study were similar based on the Factor IX component. The amount Factor IX in 2 U of FFP is approximately 500 U, and the median dose of 4PCC patients received in our study based on the Factor IX component was 500 U.[16] Compared to other published studies, our patients received lower doses of PCC. In a retrospective study comparing 3PCC to FFP in CABG and valve surgery, the median 3PCC dose was 1,500 U, and median dose of FFP was 2 U—this study did not report weight-based doses.[21] Another retrospective study comparing 4PCC to FFP during pulmonary endarterectomy with hypothermic circulatory arrest used a dose of 15 U/kg of 4PCC and 15 mL/kg of FFP.[22] The labeling for 4PCC recommends a dosing range of 25 to 50 U/kg for the reversal of acute major bleeding based on INR.[17] The upper end of this dosing range has resulted in fatal thrombus formation reported in cardiac surgery, and why 4PCC contains a Black Box warning for patients with thromboembolic disease.[17,29] With PCC becoming more widely adopted in cardiac surgery, the optimal dosing strategy for patients remains unknown and requires further investigation to ensure effective and safe doses are selected.

Despite our patients receiving lower doses of 4PCC and FFP, we found a similar effect size regarding the effectiveness of 4PCC reducing RBC transfusions as Cappabianca and colleagues who utilized propensity adjusted (OR: 0.50 CI: 0.31-0.80) and matching techniques (OR: 0.38) for their analysis.[21] Our primary endpoint included intraoperative as well as 24 hour postoperative RBC transfusion, where Cappabianca did not include intraoperative RBC transfusion in their secondary endpoint. Our study team determined that the inclusion of intraoperative RBC transfusion to be a more conservative approach for our analysis, because FFP and/or 4PCC are typically given first to mitigate

blood loss and more than one dose of FFP and/or 4PCC could be given during the procedure. The majority of doses of FFP and 4PCC occurred immediately after patients were taken off CPB, then RBC transfusions are administered based on the patient status intraoperatively as well as postoperatively. Excluding RBC transfusions administered intraoperatively, patients who received 4PCC compared to FFP also had significantly less RBC transfusions 24 hours postoperatively in an unadjusted analysis (FFP: 51.5%; 4PCC: 15.7%; p-value<0.01). In a small randomized study, Demeyere and colleagues administered 4PCC or FFP before surgery to reverse an INR > 2 and immediately after patients were taken off CPB.[20] This study found the administration of 4PCC caused faster normalization of INR as well as patients requiring less blood transfusions.[20]

In our unadjusted analysis, our study found more patients developed VTE compared to patients who did not receive FFP or 4PCC, and no differences were observed in postoperative renal failure in the 3 study groups. However, a greater proportion of patients who received 4PCC developed renal failure compared to the FFP and control groups in our study. Cappabianca and colleagues found a significant association with the administration of 3PCC administration and AKI and RRT after propensity adjustment but not after propensity score matching.[21] No thromboembolic complications or renal dysfunction was noted postoperatively in the FFP or 4PCC groups by Demeyere and colleagues.[20]

Other published literature regarding PCC use in cardiac surgery used different methodologies and study populations, which found varying results. Arnekian performed a retrospective observational study with 3 treatment groups: 4PCC, FFP, and 3PCC plus FFP for treatment of active bleeding post-cardiac surgery.[19] The 4PCC only group was found to significantly reduce blood loss based on chest-tube output compared to the FFP group. Only 1 thromboembolic event was noted in the FFP group, and postoperative renal function was not evaluated. Also, this study did not perform any multivariable analysis to control for confounding variables and selection bias.[19] In a quasi-experimental study by Görlinger and colleagues, 4PCC and FibC were administered first-line for the treatment of refractory

bleeding using a ROTEM guided algorithm.[23] This algorithmic based protocol significantly reduced allogeneic blood product transfusions after this strategy was implemented, and no significant differences were noted in thromboembolic complications before and after the adoption of the algorithm.[23] Ortmann and colleagues assessed the effectiveness and safety of 4PCC compared to FFP during pulmonary endarterectomy with hypothermic circulatory arrest.[22] This study found no difference in blood transfusion requirements in the 4PCC versus FFP groups. More patients developed postoperative renal dysfunction in the 4PCC group, but this finding was not significantly different compared to the FFP group after propensity score adjustment.[22]

None of the aforementioned studies found PCC exposure was associated with an increase in blood product utilization compared to FFP, and several studies found a significant reduction in blood transfusion requirements in cardiac surgery.[20,21,23] These findings are also consistent with *in vitro* and *ex vivo* studies comparing allogeneic blood products to synthetic factor concentrates as well as the time it takes to prepare and administer PCC products.[16-18] In an *ex vivo* study of patients receiving CPB for cardiac surgery, FibC plus recombinant Factor VIIa and FibC plus 3PCC were found to be the most efficacious to reverse coagulopathy after stopping CPB compared to FFP and FFP in combination with other products in patient blood samples.[18] The patients included in the *ex vivo* analysis did not have excessive bleeding. The effectiveness of PCC compared to FFP may also be attributed to the ability to administer PCC more quickly, potentially faster availability of the product depending on institutional workflow, and increased potency of PCC products.

STRENGTHS AND LIMITATIONS

This study contains both strengths and weaknesses that should be considered before extrapolating the results to other institutions. First, this study utilized the STS database for several safety outcomes, which researchers frequently use to evaluate cardiac surgery quality and safety. Two different multivariable analyses techniques were used to control for confounding variables and selection

bias that yielded similar results. The study groups included patients throughout the study timeframe and eliminates historical control bias encountered in quasi-experimental designs and retrospective observational studies using a historical control group. Finally, the findings of this study area based on the real-world data in the United States to evaluate 4PCC and FFP in cardiac surgery.

Like all retrospective studies, our study runs the risk of bias with any measurable or immeasurable variables unaccounted for in the analysis. These unaccounted variables may have influenced the selection of FFP and/or 4PCC, which introduces potential selection bias. In the multivariable analysis, FibC was excluded from the model, because only one exposure occurred in the FFP group. Thus, the effect of FibC could not be isolated from 4PCC in the multivariable analysis, where 20% of patients received FibC. The results also reflect the practices of a single institution with a limited sample size receiving FFP and 4PCC included in the study. The study excluded many patients to create a homogenous cohort, which needs to be considered before extrapolating to different surgery types and patient populations.

CONCLUSIONS

In patients undergoing isolated CABG and/or valve surgery, this single-center retrospective study found intraoperative administration of 4PCC compared to FFP reduced allogeneic RBC transfusions intraoperatively and within 24 hours postoperatively. Also, the administration of 4PCC should be carefully considered in patients with thromboembolic disease due to the risk of thrombosis. A large, multicenter, randomized study would provide valuable insight regarding the efficacy and safety of prothrombin complex concentrates in cardiac surgery.

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CHAPTER IV:

CONCLUSIONS AND IMPLICATIONS

The use of PCCs for the treatment of bleeding intraoperatively and postoperatively continues to increase globally, and the adoption of these products is multifactorial. Despite many technological and surgical advancements, patients who require life-saving procedures such as CABG and valve surgery will inevitably bleed due to the invasiveness of these procedures. Patients with excessive bleeding that receive blood transfusions have many complications and worse outcomes compared to patients who do not. Thus, any strategy that mitigates excessive blood loss and transfusion deserves attention, as PCCs have gained in the surgical community. Multiple studies have proven PCCs' favorable profile *in vivo* and *ex vivo* to reverse hypercoagulability. In addition, one small randomized study and several observational studies found PCC use to be safe and effective in specific cardiac procedures and patient populations. This supporting evidence has led PCCs to be recognized as a therapeutic option in clinical practice guidelines for the treatment excessive bleeding in surgery.

In our study, we found an increasing use of 4PCC in cardiac surgery with many factors predictive of 4PCC use intraoperatively such as patients with HTN. In some circumstances, providers show a preference for using FFP compared to 4PCC such as in patients with liver dysfunction. Knowing where providers choose to administer 4PCC versus FFP will help optimize the effective and safe use of these products and improve future prescribing patterns.

Finally, this study found 4PCC compared to FFP to reduce RBC transfusion requirements in patients receiving isolated CABG and/or valve surgery requiring CPB, and 4PCC may increase the risk of VTE compared to patients not receiving 4PCC or FFP. Ultimately, a well-designed, randomized clinical trial needs to be performed to confirm the clinical utility of PCC use in cardiac surgery for the treatment

of excessive bleeding. Currently, a randomized clinical trial is assessing PCC versus FFP in cardiac surgery, which is expected to finish in 2018.

TABLES

CHAPTER II TABLES

Table 1. Comparison of Patient Baseline Characteristics

Variable	Control/None (n=690)	FFP (n=68)	4PCC (n=166)	FFP v None p-value	4PCC v None p-value	FFP v 4PCC p-value
Age, mean ± sd	65.5 ± 11.4	65.9 ± 10.9	67.1 ± 12.5	0.7954	0.1011	0.4647
Male, n (%)	208 (30.1)	45 (66.2)	111 (66.9)	0.5295	0.4538	0.9189
Race						
White, n (%)	513 (74.4)	42 (61.8)	114 (68.7)	0.1241	0.2727	0.6048
Black, n (%)	49 (7.1)	7 (10.3)	17 (10.2)			
Asian, n (%)	24 (3.5)	3 (4.4)	4 (2.4)			
Other, n (%)	104 (15.1)	16 (23.5)	31 (18.7)			
BMI (kg/m^2), mean ± sd	29.5 ± 5.7	28.8 ± 12.5	28.0 ± 5.8	0.6643	0.0024	0.5976
Surgeon 1, n (%)	264 (38.3)	29 (42.7)	90 (54.2)	0.428	0.005	0.3095
Surgeon 2, n (%)	138 (20.0)	9 (13.2)	15 (9.0)			
Surgeon 3, n (%)	113 (16.4)	8 (11.8)	23 (13.9)			
Surgeon 4, n (%)	60 (8.7)	9 (13.2)	11 (6.6)			
Surgeon 5, n (%)	55 (8.0)	8 (11.8)	12 (7.2)			
Surgeon 6, n (%)	47 (6.8)	3 (4.4)	12 (7.2)			
Surgeon Other, n (%)	13 (1.9)	2 (2.9)	3 (1.8)			
Surgery type						
CABG, n (%)	392 (56.8)	33 (48.5)	50 (30.1)	0.2808	<0.0001	0.0202
Valve, n (%)	247 (35.8)	27 (39.7)	97 (58.4)			
CABG + valve, n (%)	51 (7.4)	8 (11.8)	19 (11.5)			
Graft count						
0, n (%)	247 (35.8)	27 (39.7)	97 (58.4)	0.2726	<0.0001	0.0437
1, n (%)	44 (6.4)	1 (1.5)	7 (4.2)			
2, n (%)	95 (13.8)	13 (19.1)	18 (10.8)			
3, n (%)	233 (33.8)	23 (33.8)	37 (22.3)			
≥ 4, n (%)	71 (10.3)	4 (5.9)	7 (4.2)			
Open chest repeat, n (%)	68 (9.9)	14 (20.6)	40 (24.1)	0.0066	<0.0001	0.5631
Preop status (non-elective), n (%)	228 (33.0)	35 (51.5)	76 (45.8)	0.0023	0.0021	0.4289
Comorbidities						
Arrhythmia, n (%)	174 (25.2)	17 (25.0)	52 (31.3)	0.9686	0.109	0.3353
Cancer (within 5 years), n (%)	37 (5.4)	1 (1.5)	8 (4.9)	0.2422	0.7876	0.2904
Cerebrovascular disease, n (%)	130 (18.8)	21 (30.9)	33 (19.9)	0.0177	0.7595	0.0697
Chronic lung disease, n (%)						
None	535 (77.5)	56 (82.4)	121 (72.9)	0.4113	---	---
Mild	79 (11.5)	5 (7.4)	23 (13.9)			

Moderate	32 (4.6)	2 (2.9)	10 (6.0)			
Severe	24 (3.5)	5 (7.4)	5 (3.0)			
Unknown severity	16 (2.3)	0 (0)	5 (3.0)			
Unknown	4 (0.6)	0 (0)	2 (1.2)			
Coronary artery disease, n (%)	85 (12.4)	4 (5.9)	11 (6.6)	0.1646	0.0351	1
DM, n (%)	270 (39.1)	30 (44.1)	57 (34.3)	0.4223	0.2538	0.1599
Dyslipidemia, n (%)	555 (80.4)	56 (82.4)	111 (66.9)	0.7027	0.0002	0.0173
Heart failure, n (%)	191 (27.8)	27 (39.7)	64 (38.6)	0.0381	0.0064	0.8697
Hemodialysis, n (%)	35 (5.1)	8 (11.8)	14 (8.4)	0.0228	0.0942	0.428
Hypertension, n (%)	615 (89.1)	56 (82.4)	143 (86.1)	0.0944	0.278	0.4603
Immunocompromised, n (%)	43 (6.2)	7 (10.3)	14 (8.4)	0.1979	0.307	0.6512
Liver disease, n (%)	52 (7.6)	14 (20.6)	16 (9.6)	0.0003	0.3713	0.0229
Myocardial infarction, n (%)	214 (31.1)	25 (36.8)	45 (27.1)	0.3342	0.32	0.143
Peripheral arterial disease, n (%)	80 (11.6)	11 (16.2)	24 (14.5)	0.2673	0.3106	0.7379
Pneumonia, n (%)	51 (7.4)	4 (5.9)	16 (9.6)	0.8089	0.347	0.446
Sleep Apnea, n (%)	94 (13.6)	3 (4.4)	16 (9.6)	0.0342	0.1666	0.2907
Medications prior to surgery						
Anticoag. within 48 hours, n (%)	135 (19.6)	18 (26.5)	50 (30.1)	0.1759	0.003	0.5766
Antiplatelet within 5 days, n (%)	64 (9.3)	4 (5.9)	9 (5.4)	0.5034	0.1105	1
Aspirin, n (%)	276 (40.2)	27 (39.7)	68 (41.2)	0.94	0.8073	0.884
Inotrope, n (%)	4 (0.6)	2 (2.9)	4 (2.4)	0.0939	0.05	1
Preoperative labs						
CVP						
0-3	282 (41.1)	29 (43.3)	61 (37.0)	0.487	0.007	0.625
4-9	318 (46.3)	26 (38.8)	66 (40.0)			
10-15	64 (9.3)	8 (11.9)	30 (18.2)			
> 15	23 (3.4)	4 (6.0)	8 (4.9)			
Hematocrit (%), mean ± sd	39 ± 5.6	37.4 ± 7.0	36.1 ± 6.3	0.0666	<0.0001	0.1896
INR, mean ± sd	1.07 ± 0.13	1.13 ± 0.14	1.18 ± 0.21	0.0004	<0.0001	0.0683
LVEF (%), mean ± sd	56.0 ± 11.7	53.5 ± 14.0	54.6 ± 13.1	0.1581	0.2089	0.5679
Platelet (10^9/L), mean ± sd	215 ± 65	197 ± 83	197 ± 64	0.0852	0.0018	0.9644
SCr (mg/dL), mean ± sd	1.3 ± 1.3	1.7 ± 1.2	1.5 ± 1.6	0.1483	0.0918	0.5872
Intraoperative measures						
FFP dose (mL/kg)/ 4PCC dose (unit/kg), mean ± sd	---	5.9 ± 3.4	9.0 ± 5.8	---	---	---
FFP dose units/4PCC dose units, median (Q1,Q3)	---	2 (1,2)	500 (500,1000)	---	---	---
4PCC/FFP time given to surgery end (hr), mean ± sd	---	1.2 ± 1.0	1.0 ± 0.5	---	---	0.109

Surgery duration (hr), mean ± sd	3.9 ± 1.1	4.6 ± 1.4	4.4 ± 1.2	<0.0001	<0.0001	0.1933
Cell saver use (units), mean ± sd	2.0 ± 1.1	2.4 ± 1.2	2.8 ± 1.5	0.0032	<0.0001	0.055
CPB time (min), mean ± sd	86 ± 35	97.9 ± 34.3	100.2 ± 47.1	0.0074	<0.0001	0.7123
ACT time (min), mean ± sd	67.8 ± 28.4	79.0 ± 29.7	78.7 ± 33.3	0.0024	<0.0001	0.9422
Intraoperative medications						
Antithrombin III, n (%)	35 (5.1)	3 (4.4)	12 (7.2)	1	0.2735	0.563
Desmopressin, n (%)	152 (22.0)	24 (35.3)	84 (50.0)	0.0134	<0.0001	0.0403
EACA, n (%)	659 (95.5)	65 (95.6)	155 (93.4)	1	0.2532	0.7625
FibC, n (%)	2 (0.3)	1 (1.5)	33 (19.9)	0.246	<0.0001	<0.0001

Table 2. Factors Associated with Use of 4PCC excluding patients who received FFP intraoperatively

Variable	Odds ratio	95% CI Interval		p-value
Predisposing factors				
Age	1.026	1.005	1.048	0.0146
Female (ref male)	0.608	0.365	1.013	0.056
Race (ref white)				
Black	1.126	0.488	2.598	0.8509
Asian	1.385	0.401	4.784	0.7675
Other	1.339	0.735	2.438	0.6962
Enabling factors				
Emergent procedure	1.445	0.824	2.536	0.199
Surgeon (ref 1)				
Surgeon 2	0.32	0.144	0.711	0.5425
Surgeon 3	0.296	0.132	0.663	0.3521
Surgeon 4	0.232	0.086	0.623	0.1705
Surgeon 5	0.42	0.173	1.02	0.8837
Surgeon 6	0.546	0.203	1.47	0.4775
Surgeon Other	0.318	0.064	1.581	0.7355
Need factors				
BMI	0.937	0.897	0.979	0.0037
CABG + Valve	0.729	0.352	1.51	0.3953
Repeat chest	1.716	0.923	3.192	0.0881
Arrhythmia	0.552	0.32	0.952	0.0325
CAD	0.808	0.358	1.823	0.608
CVD	0.913	0.523	1.594	0.75
DM	0.671	0.405	1.11	0.1204
Dyslipidemia	0.486	0.277	0.854	0.012
HF	1.134	0.688	1.869	0.6225
HTN	1.37	0.66	2.844	0.3985
Immunocompromised	1.316	0.573	3.025	0.5171
Liver dysfunction	0.543	0.233	1.266	0.1575
MI	0.864	0.5	1.494	0.6011
PAD	1.557	0.802	3.024	0.1912
PNA	0.651	0.29	1.461	0.298
Anticoag. within 48 hours	1.009	0.54	1.885	0.9768
Anti-plt within 5 days	1.072	0.427	2.691	0.8828
Aspirin	1.414	0.829	2.411	0.204
CVP (ref 4-9)				
CVP: 0-3	1.192	0.734	1.938	0.6599
CVP: 10-15	1.682	0.805	3.513	0.3669

CVP: > 15	1.441	0.491	4.232	0.805
HCT preop (%)	0.914	0.873	0.957	0.0001
INR preop	16.109	4.042	64.208	<0.0001
LVEF (%)	0.994	0.976	1.013	0.5513
Plt preop (ref plt < 150, 10^9/L)	0.548	0.315	0.953	0.0333
SCr preop (mg/dL)	0.918	0.772	1.091	0.3315
Cell saver use (unit)	1.816	1.49	2.214	<0.0001
CPB time (min)	1.016	1.008	1.024	<0.0001
Antithrombin III intraop	0.901	0.374	2.169	0.8159
EACA intraop	0.341	0.144	0.807	0.0143
Desmopressin intraop	3.507	2.209	5.566	<0.0001

C-statistic=0.851; Hosmer-Lemeshow=0.0659

Table 3. Factors Associated with Use of FFP excluding patients who received 4PCC intraoperatively

Variable	Odds ratio	95% CI Interval		p-value
Predisposing Factors				
Age	1.012	0.985	1.04	0.3738
Female (ref male)	1.15	0.59	2.24	0.6818
Race (ref white)				
Black	0.804	0.268	2.413	0.3884
Asian	1.319	0.321	5.415	0.823
Other	1.759	0.871	3.556	0.2107
Enabling Factors				
Emergent procedure	2.234	1.115	4.477	0.0235
Surgeon (ref 1)				
Surgeon 2	0.504	0.197	1.291	0.4875
Surgeon 3	0.538	0.188	1.538	0.608
Surgeon 4	0.868	0.305	2.466	0.533
Surgeon 5	0.629	0.201	1.967	0.8924
Surgeon 6	0.587	0.145	2.384	0.8292
Surgeon Other	0.699	0.124	3.935	0.9556
Need Factors				
BMI	0.999	0.951	1.05	0.9773
CABG + Valve	1.414	0.528	3.789	0.4907
Repeat chest	1.716	0.787	3.742	0.1748
Arrhythmia	0.754	0.367	1.55	0.4428
CAD	0.546	0.176	1.691	0.2939
CVD	2.123	1.106	4.076	0.0236
DM	1.22	0.636	2.339	0.5496
Dyslipidemia	1.323	0.562	3.114	0.521
HF	1.292	0.679	2.46	0.4346
HTN	0.458	0.188	1.118	0.0863
Immunocompromised	1.051	0.353	3.127	0.9286
Liver dysfunction	2.004	0.855	4.699	0.1099
MI	1.157	0.596	2.247	0.6666
PAD	1.295	0.57	2.938	0.5369
PNA	0.609	0.235	1.582	0.3084
Anticoag. within 48 hours	0.899	0.392	2.061	0.8011
Anti-plt within 5 days	0.669	0.203	2.201	0.5085
Aspirin	1.09	0.535	2.221	0.8124
CVP (ref 4-9)				
CVP: 0-3	0.768	0.405	1.457	0.4488
CVP: 10-15	0.665	0.239	1.851	0.3761

CVP: > 15	1.537	0.408	5.788	0.3323
HCT preop (%)	0.99	0.932	1.052	0.7479
INR preop	5.309	0.716	39.381	0.1025
LVEF (%)	0.991	0.967	1.015	0.4664
Plt preop (ref plt < 150, 10^9/L)	0.684	0.322	1.453	0.3229
SCr preop (mg/dL)	1.145	0.961	1.365	0.1304
Cell saver use (unit)	1.415	1.1	1.819	0.0068
CPB time (min)	1.005	0.995	1.016	0.3278
Antithrombin III intraop	0.627	0.159	2.465	0.5036
EACA intraop	0.702	0.187	2.638	0.6007
Desmopressin intraop	1.675	0.883	3.177	0.114

C-statistic= 0.777; Hosmer-Lemeshow=0.4826

Table 4. Comparison of factors predicting the use of 4PCC versus FFP intraoperatively

Variable	Odds Ratio	95% CI Interval		p-value
Predisposing Factors				
Female (ref male)	0.575	0.275	1.203	0.1416
Enabling Factors				
Emergent procedure	0.502	0.248	1.016	0.0555
Need Factors				
BMI	0.97	0.936	1.006	0.1055
CVD	0.525	0.251	1.101	0.088
Dyslipidemia	0.428	0.185	0.99	0.0474
HTN	2.584	1.013	6.596	0.047
Immunocompromised	2.466	0.678	8.964	0.1706
Liver dysfunction	0.163	0.056	0.475	0.0009
HCT preop (%)	0.919	0.864	0.978	0.0074
INR preop	5.393	0.686	42.4	0.1092
SCr preop (mg/dL)	0.852	0.703	1.032	0.1022
Cell saver use (unit)	1.316	1.007	1.721	0.0441
CPB time (min)	1.005	0.998	1.013	0.1528
Desmopressin intraop	2.264	1.143	4.481	0.019

C-statistic= 0.753; Hosmer-Lemeshow=0.8418

CHAPTER III TABLES

Table 1. Comparison of Patient Baseline Characteristics

Variable	Control/None (n=690)	FFP (n=68)	4PCC (n=166)	FFP v None p-value	4PCC v None p-value	FFP v 4PCC p-value
Age, mean ± sd	65.5 ± 11.4	65.9 ± 10.9	67.1 ± 12.5	0.7954	0.1011	0.4647
Male, n (%)	208 (30.1)	45 (66.2)	111 (66.9)	0.5295	0.4538	0.9189
Race						
White, n (%)	513 (74.4)	42 (61.8)	114 (68.7)	0.1241	0.2727	0.6048
Black, n (%)	49 (7.1)	7 (10.3)	17 (10.2)			
Asian, n (%)	24 (3.5)	3 (4.4)	4 (2.4)			
Other, n (%)	104 (15.1)	16 (23.5)	31 (18.7)			
BMI (kg/m^2), mean ± sd	29.5 ± 5.7	28.8 ± 12.5	28.0 ± 5.8	0.6643	0.0024	0.5976
Surgeon 1, n (%)	264 (38.3)	29 (42.7)	90 (54.2)	0.428	0.005	0.3095
Surgeon 2, n (%)	138 (20.0)	9 (13.2)	15 (9.0)			
Surgeon 3, n (%)	113 (16.4)	8 (11.8)	23 (13.9)			
Surgeon 4, n (%)	60 (8.7)	9 (13.2)	11 (6.6)			
Surgeon 5, n (%)	55 (8.0)	8 (11.8)	12 (7.2)			
Surgeon 6, n (%)	47 (6.8)	3 (4.4)	12 (7.2)			
Surgeon Other, n (%)	13 (1.9)	2 (2.9)	3 (1.8)			
Surgery type						
CABG, n (%)	392 (56.8)	33 (48.5)	50 (30.1)	0.2808	<0.0001	0.0202
Valve, n (%)	247 (35.8)	27 (39.7)	97 (58.4)			
CABG + valve, n (%)	51 (7.4)	8 (11.8)	19 (11.5)			
Graft count						
0, n (%)	247 (35.8)	27 (39.7)	97 (58.4)	0.2726	<0.0001	0.0437
1, n (%)	44 (6.4)	1 (1.5)	7 (4.2)			
2, n (%)	95 (13.8)	13 (19.1)	18 (10.8)			
3, n (%)	233 (33.8)	23 (33.8)	37 (22.3)			
≥ 4, n (%)	71 (10.3)	4 (5.9)	7 (4.2)			
Open chest repeat, n (%)	68 (9.9)	14 (20.6)	40 (24.1)	0.0066	<0.0001	0.5631
Preop status (non-elective), n (%)	228 (33.0)	35 (51.5)	76 (45.8)	0.0023	0.0021	0.4289
Comorbidities						
Arrhythmia, n (%)	174 (25.2)	17 (25.0)	52 (31.3)	0.9686	0.109	0.3353
Cancer (within 5 years), n (%)	37 (5.4)	1 (1.5)	8 (4.9)	0.2422	0.7876	0.2904
Cerebrovascular disease, n (%)	130 (18.8)	21 (30.9)	33 (19.9)	0.0177	0.7595	0.0697
Chronic lung disease, n (%)						
None	535 (77.5)	56 (82.4)	121 (72.9)	0.4113	---	---
Mild	79 (11.5)	5 (7.4)	23 (13.9)			

Moderate	32 (4.6)	2 (2.9)	10 (6.0)			
Severe	24 (3.5)	5 (7.4)	5 (3.0)			
Unknown severity	16 (2.3)	0 (0)	5 (3.0)			
Unknown	4 (0.6)	0 (0)	2 (1.2)			
Coronary artery disease, n (%)	85 (12.4)	4 (5.9)	11 (6.6)	0.1646	0.0351	1
DM, n (%)	270 (39.1)	30 (44.1)	57 (34.3)	0.4223	0.2538	0.1599
Dyslipidemia, n (%)	555 (80.4)	56 (82.4)	111 (66.9)	0.7027	0.0002	0.0173
Heart failure, n (%)	191 (27.8)	27 (39.7)	64 (38.6)	0.0381	0.0064	0.8697
Hemodialysis, n (%)	35 (5.1)	8 (11.8)	14 (8.4)	0.0228	0.0942	0.428
Hypertension, n (%)	615 (89.1)	56 (82.4)	143 (86.1)	0.0944	0.278	0.4603
Immunocompromised, n (%)	43 (6.2)	7 (10.3)	14 (8.4)	0.1979	0.307	0.6512
Liver disease, n (%)	52 (7.6)	14 (20.6)	16 (9.6)	0.0003	0.3713	0.0229
Myocardial infarction, n (%)	214 (31.1)	25 (36.8)	45 (27.1)	0.3342	0.32	0.143
Peripheral arterial disease, n (%)	80 (11.6)	11 (16.2)	24 (14.5)	0.2673	0.3106	0.7379
Pneumonia, n (%)	51 (7.4)	4 (5.9)	16 (9.6)	0.8089	0.347	0.446
Sleep Apnea, n (%)	94 (13.6)	3 (4.4)	16 (9.6)	0.0342	0.1666	0.2907
Medications prior to surgery						
Anticoag. within 48 hours, n (%)	135 (19.6)	18 (26.5)	50 (30.1)	0.1759	0.003	0.5766
Antiplatelet within 5 days, n (%)	64 (9.3)	4 (5.9)	9 (5.4)	0.5034	0.1105	1
Aspirin, n (%)	276 (40.2)	27 (39.7)	68 (41.2)	0.94	0.8073	0.884
Inotrope, n (%)	4 (0.6)	2 (2.9)	4 (2.4)	0.0939	0.05	1
Preoperative labs						
CVP						
0-3	282 (41.1)	29 (43.3)	61 (37.0)	0.487	0.007	0.625
4-9	318 (46.3)	26 (38.8)	66 (40.0)			
10-15	64 (9.3)	8 (11.9)	30 (18.2)			
> 15	23 (3.4)	4 (6.0)	8 (4.9)			
Hematocrit (%), mean ± sd	39 ± 5.6	37.4 ± 7.0	36.1 ± 6.3	0.0666	<0.0001	0.1896
INR, mean ± sd	1.07 ± 0.13	1.13 ± 0.14	1.18 ± 0.21	0.0004	<0.0001	0.0683
LVEF (%), mean ± sd	56.0 ± 11.7	53.5 ± 14.0	54.6 ± 13.1	0.1581	0.2089	0.5679
Platelet (10^9/L), mean ± sd	215 ± 65	197 ± 83	197 ± 64	0.0852	0.0018	0.9644
SCr (mg/dL), mean ± sd	1.3 ± 1.3	1.7 ± 1.2	1.5 ± 1.6	0.1483	0.0918	0.5872
Intraoperative measures						
FFP dose (mL/kg)/ 4PCC dose (unit/kg), mean ± sd	---	5.9 ± 3.4	9.0 ± 5.8	---	---	---
FFP dose units/4PCC dose units, median (Q1,Q3)	---	2 (1,2)	500 (500,1000)	---	---	---
4PCC/FFP time given to surgery end (hr), mean ± sd	---	1.2 ± 1.0	1.0 ± 0.5	---	---	0.109

Surgery duration (hr), mean ± sd	3.9 ± 1.1	4.6 ± 1.4	4.4 ± 1.2	<0.0001	<0.0001	0.1933
Cell saver use (units), mean ± sd	2.0 ± 1.1	2.4 ± 1.2	2.8 ± 1.5	0.0032	<0.0001	0.055
CPB time (min), mean ± sd	86 ± 35	97.9 ± 34.3	100.2 ± 47.1	0.0074	<0.0001	0.7123
ACT time (min), mean ± sd	67.8 ± 28.4	79.0 ± 29.7	78.7 ± 33.3	0.0024	<0.0001	0.9422
Intraoperative medications						
Antithrombin III, n (%)	35 (5.1)	3 (4.4)	12 (7.2)	1	0.2735	0.563
Desmopressin, n (%)	152 (22.0)	24 (35.3)	84 (50.0)	0.0134	<0.0001	0.0403
EACA, n (%)	659 (95.5)	65 (95.6)	155 (93.4)	1	0.2532	0.7625
FibC, n (%)	2 (0.3)	1 (1.5)	33 (19.9)	0.246	<0.0001	<0.0001

Table 2. Unadjusted Analysis of Patient Effectiveness Outcomes for Exposure Groups

Outcomes	Control (n=690)	FFP (n=68)	4PCC (n=166)	FFP v None p-value	4PCC v None p-value	FFP v 4PCC p-value
Intraoperative EBL (mL), mean ± sd	1126 ± 459	1382 ± 620	1459 ± 642	0.0025	<0.0001	0.4268
Postop Hgb (g/dL), mean ± sd	9.6 ± 1.6	7.9 ± 1.4	8.9 ± 1.4	<0.0001	<0.0001	<0.0001
Post-operative Plt, 10^9/L	123 ± 44	105 ± 96	119 ± 114	0.0011	0.2552	0.0071
Transfusion requirements						
RBC, n (%)	94 (13.6)	53 (77.9)	100 (60.2)	<0.0001	<0.0001	0.0098
RBC (units), mean ± sd	0.2 ± 0.6	2.0 ± 1.7	1.3 ± 1.9	<0.0001	<0.0001	0.0104
RBC 24 hr postop, n (%)	53 (7.7)	35 (51.5)	26 (15.7)	<0.0001	0.0024	<0.0001
FFP 24 hr postop, n (%)	32 (4.6)	6 (8.8)	17 (10.2)	0.2232	0.0092	0.8141
Plt, n (%)	6 (0.9)	20 (29.4)	14 (8.4)	<0.0001	<0.0001	<0.0001
Cryoprecipitate, n (%)	37 (5.4)	14 (20.6)	23 (13.9)	<0.0001	0.0001	0.2

Table 3. Effect of 4PCC versus FFP on RBC Transfusion in Cardiac Surgery: Logistic Regression

Variable	Odds ratio	95% CI Interval		p-value
4PCC (ref FFP)	0.281	0.127	0.621	0.0017
BMI	0.954	0.902	1.01	0.105
Surgeon (ref 1)				
Surgeon 2	0.2	0.059	0.68	0.7201
Surgeon 3	0.149	0.043	0.513	0.3152
Surgeon 4	0.289	0.075	1.112	0.7551
Surgeon 5	0.177	0.039	0.808	0.6194
Surgeon 6	0.37	0.098	1.391	0.4791
Surgeon Other	0.087	0.006	1.237	0.354
CABG + Valve	3.708	0.922	14.915	0.065
CVD	2.533	1.034	6.206	0.0422
DM	1.942	0.887	4.251	0.0971
HF	2.097	1.006	4.371	0.0481
HCT preop (%)	0.957	0.904	1.012	0.1252
LVEF (%)	0.981	0.955	1.008	0.1603
Plt preop (ref plt < 150, 10^9/L)	0.524	0.224	1.228	0.1371
Cell saver use (unit)	1.323	1.002	1.747	0.0484
CPB time (min)	1.025	1.013	1.037	<0.0001
Antithrombin III intraop	0.33	0.085	1.279	0.1087

Backward elimination regression of p-value < 0.2

C-statistic=0.803; Hosmer-Lemeshow=0.594

Table 4. Effect of 4PCC versus FFP in the proportion of patients requiring RBC transfusion during and post-cardiac surgery: Sensitivity Analysis

Variable	Odds ratio	95% CI Interval		p-value
4PCC (ref FFP)	0.41	0.19	0.89	0.023
Propensity score	1.09	0.25	4.73	0.907

C-statistic=0.623; Hosmer-Lemeshow=0.549

Table 5. Unadjusted Analysis of Patient Safety Outcomes for Exposure Groups

Safety Outcomes	Control (n=690)	FFP (n=68)	4PCC (n=166)	FFP v None p-value	4PCC v None p-value	FFP v 4PCC p-value
Composite safety outcome (VTE, stroke/TIA, cardiac arrest)	58 (8.4)	5 (7.4)	18 (10.8)	0.9943	0.4013	0.5670
VTE/PE, n (%)	20 (2.9)	2 (2.9)	14 (8.4)	1	0.001	0.1617
Stroke/TIA, n (%)	13 (1.9)	0 (0)	5 (3.0)	0.6197	0.3631	0.325
Cardiac arrest	25 (3.6)	3 (4.4)	5 (3.0)	0.7324	0.7007	0.6941
OR return, n (%)	37 (5.4)	23 (13.9)	14 (20.6)	<0.0001	0.0002	0.2327
Reoperation due to bleed, n (%)	9 (1.3)	3 (4.4)	4 (2.4)	0.0844	0.2924	0.4175
Renal failure, n (%)	17 (2.5)	2 (2.9)	8 (4.8)	0.6849	0.1056	0.7278
LOS after surgery (days), median (Q1,Q3)	8 (6,11)	11 (8,13.5)	11 (8,15)	<0.0001	<0.0001	0.5412
LOS (days), median (Q1,Q3)	9 (7,13)	13 (10,18.5)	14 (9,20)	<0.0001	<0.0001	<0.0001
Death, n (%)	16 (2.3)	2 (2.9)	3 (1.8)	0.6717	1	0.6296

FIGURES

Figure 1. Patient Consort Diagram

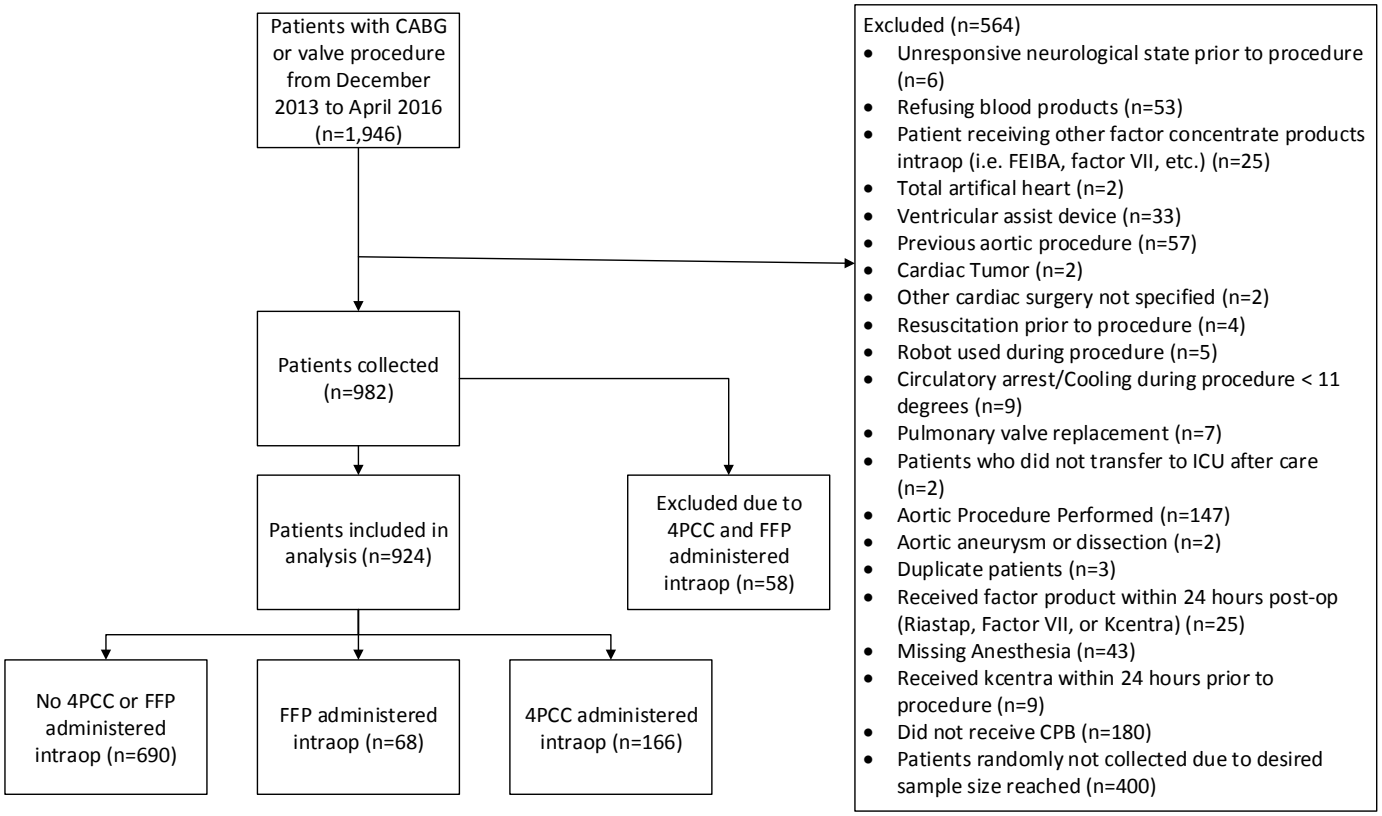
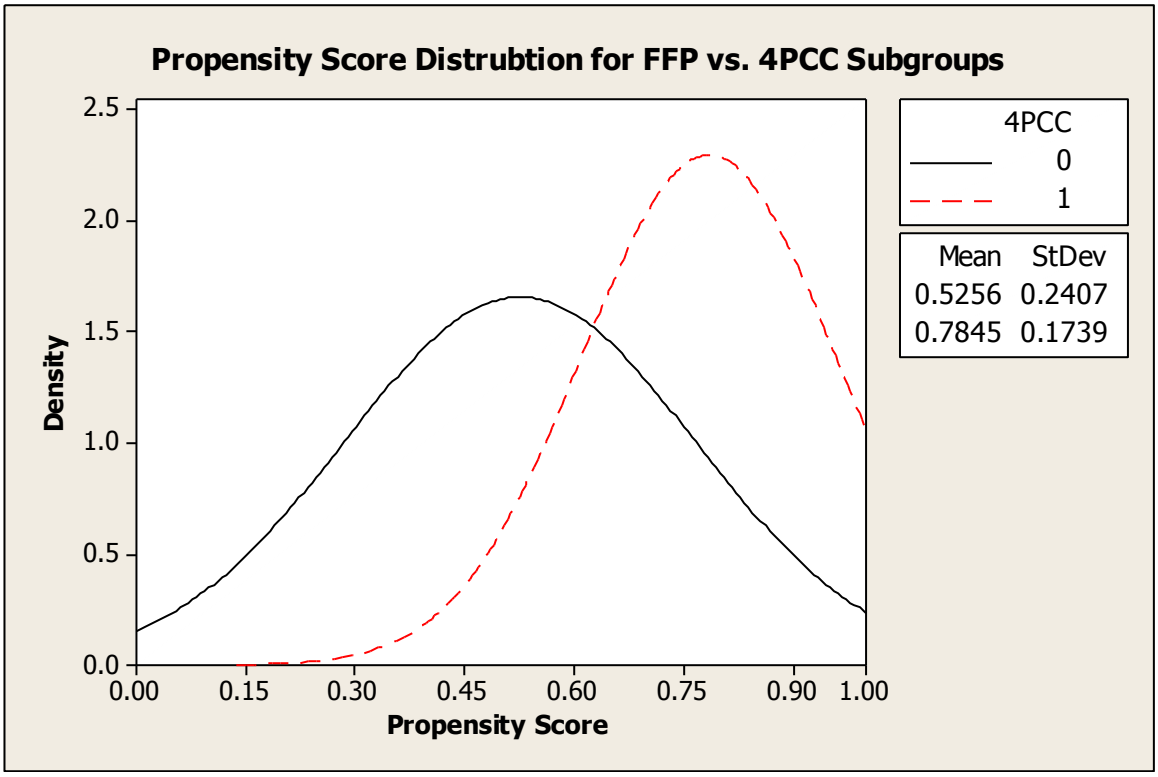


Figure 2. Propensity Score Overlap and Distribution for Sensitivity Analysis



APPENDIX

Table 1. ICD-10 Procedure Codes for CABG

Section	**0**	Medical and Surgical	
Body System	**2**	Heart and Great Vessels	
Operation	**1**	Bypass: Altering the route of passage of the contents of a tubular body part	
Body Part	***Approach***	***Device***	***Qualifier***
0 Coronary Artery, One Site **1** Coronary Artery, Two Sites **2** Coronary Artery, Three Sites **3** Coronary Artery, Four or More Sites	**0** Open	**9** Autologous Venous Tissue **A** Autologous Arterial Tissue **J** Synthetic Substitute **K** Nonautologous Tissue Substitute	**3** Coronary Artery **8** Internal Mammary, Right **9** Internal Mammary, Left **C** Thoracic Artery **F** Abdominal Artery **W** Aorta
0 Coronary Artery, One Site **1** Coronary Artery, Two Sites **2** Coronary Artery, Three Sites **3** Coronary Artery, Four or More Sites	**0** Open	**Z** No Device	**3** Coronary Artery **8** Internal Mammary, Right **9** Internal Mammary, Left **C** Thoracic Artery **F** Abdominal Artery

Table 2. Valve Repair ICD-10 Procedure Codes

Section	**0**	Medical and Surgical	
Body System	**2**	Heart and Great Vessels	
Operation	**Q**	Repair: Restoring, to the extent possible, a body part to its normal anatomic structure and function	
Part	**Approach**	**Device**	**Qualifier**
F Aortic Valve **G** Mitral Valve **H** Pulmonary Valve **J** Tricuspid Valve	**0** Open	**Z** No Device	**Z** No Qualifier

Table 3. Valve Replacement ICD-10 Procedure Codes

Section	**0**	Medical and Surgical	
Body System	**2**	Heart and Great Vessels	
Operation	**R**	Replacement: Putting in or on biological or synthetic material that physically takes the place and/or function of all or a portion of a body part	
Part	**Approach**	**Device**	**Qualifier**

F Aortic Valve **G** Mitral Valve **H** Pulmonary Valve **J** Tricuspid Valve	**0** Open	**7** Autologous Tissue Substitute **8** Zooplastic Tissue **J** Synthetic Substitute **K** Nonautologous Tissue Substitute	**Z** No Qualifier